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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR §1.53(c).

INVENTOR(S)				
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<input type="checkbox"/> Additional inventors are being named on the separately numbered sheets attached hereto.				
TITLE OF THE INVENTION (280 characters max) SOMATOSTATIN VECTORS				
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<input type="checkbox"/> Customer Number:		Place Customer Number Bar Code Label Here		
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ENCLOSED APPLICATION PARTS (check all that apply)				
<input checked="" type="checkbox"/> Specification	Number of Pages	402	<input type="checkbox"/> CD(S), Number	
<input type="checkbox"/> Drawing(s)	Number of Sheets		<input checked="" type="checkbox"/> Other (specify)	Claims: 9 pages.
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76.				
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)				
<input type="checkbox"/> Applicant Claims small entity status. See 37 CFR 1.27.			FILING FEE AMOUNT (\$)	
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees.				
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:			50-0590	\$160.00
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.				
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.				
<input checked="" type="checkbox"/> No.				
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are:				

Respectfully submitted,

Alan F. Feeney
Signature

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Reg. No. 43,609

Date 4-22-2003

Telephone No. 508/478-0144

Docket No. 119P

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PROVISIONAL APPLICATION
UNDER 37 C.F.R. § 1.53(c)

APPLICANT: ZHENG XIN DONG ET AL.

TITLE: SOMATOSTATIN VECTORS

PATENT

ATTORNEY DOCKET NO: 119P

**METHODS AND COMPOSITIONS FOR THE
TARGETED DELIVERY OF CYTOTOXIC AGENTS**

FIELD OF THE INVENTION

[0001] The present invention relates to therapeutic compositions and their use in the treatment of disease states. More particularly, the present invention provides compounds, compositions and methods for treating disease states associated with aberrant or undesirable cellular proliferation, migration, and/or physiological activity.

BACKGROUND OF THE INVENTION

[0002] Most cytotoxic drugs exhibit undesirable toxic side effects due to their lack of selective action toward the tissues or cells requiring therapeutic effect. Various approaches have been pursued to achieve the selective delivery of cytotoxic agents to a target cell type.

[0003] Using biological receptor ligands as carriers of drugs to target these drugs to the cells of interest can reduce toxic side-effects and greatly improve the efficiency drug delivery. For example, International Patent Publication No. WO97/19954 discloses conjugates of an anthracycline cytotoxic agent such as doxorubicin with a peptide hormone such as LHRH, bombesin or somatostatin. The cytotoxic agent is covalently attached to the peptide via a linker of formula $-C(O)-(CH_2)_n-C(O)-$, $n = 0-7$.

[0004] Similarly, European Patent Application No. EP1118336 discloses conjugates of somatostatin analogs, e.g., octreotide, lanreotide, and vapreotide, and a cytotoxic drug, such as paclitaxel, doxorubicin, or camptothecin, through a spacer, wherein the spacer is also indicated to have the structure: $-C(O)-(CH_2)_n-C(O)-$, $n = 0-7$.

[0005] U.S. Patent Application Publication No. 2002/0115596 discloses conjugates of cytotoxic agents and oligopeptides in which the amino acid sequences of the peptides are indicated to be cleaved preferentially by free prostate specific antigen. Such conjugates are said to be useful for the treatment of prostate cancer and benign prostatic hyperplasia.

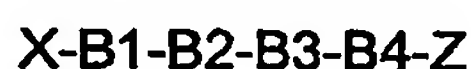
[0006] U.S. Patent Application Publication No. 2003/0064984 discloses conjugates of cytotoxic analogs of CC-1065 and the duocarmycins with cleavable linker arms and a targeting agent such as an antibody or a peptide. The cytotoxic analogs are indicated to be released upon cleavage of the linker.

[0007] International Patent Application No. WO02/34237 discloses conjugates of active agents covalently attached directly to a polypeptide. The polypeptide is said to stabilize the active agent, e.g., in the stomach, through conformational protection.

[0008] There remains, however, a significant need for targeted cytotoxic drugs with improved properties in respect of targeting specificity, systemic toxicity, and pharmacokinetics.

SUMMARY OF THE INVENTION

[0009] The instant invention provides compounds comprising a cytotoxic moiety bound to a targeting moiety via a linker, e.g., as described by formula I:



(I)

[010] wherein:

[011] X is a cytotoxic or cytostatic agent;

[012] each of B^1 , B^2 , B^3 , and B^4 is, independently for each occurrence, $(\text{Doc})_m$, $(\text{Aepa})_n$, $-(\text{C}(\text{O})\text{-A}^1\text{-A}^2\text{-A}^3\text{-A}^4\text{-A}^5\text{-C}(\text{O}))_s$ - or $(\text{amino acid})_p$,

[013] each of A^1 and A^5 is, independently for each occurrence, CR^1R^2 ;

[014] each of R^1 and R^2 is, independently for each occurrence, H, F, Br, Cl, I, $\text{C}_{(1-30)}\text{alkyl}$, $\text{C}_{(2-30)}\text{alkenyl}$, substituted $\text{C}_{(1-30)}\text{alkyl}$, substituted $\text{C}_{(2-30)}\text{alkenyl}$, SR^3 , $\text{S}(\text{O})\text{R}^4$, or $\text{S}(\text{O})_2\text{R}^5$, or R^1 and R^2 together can form a $\text{C}_{(3-30)}\text{cycloalkyl}$, $\text{C}_{(3-30)}\text{heterocycle}$, or $\text{C}_{(5-30)}\text{aryl}$ ring;

[015] each of R^3 , R^4 , and R^5 is, independently for each occurrence, $\text{C}_{(1-30)}\text{alkyl}$, $\text{C}_{(2-30)}\text{alkenyl}$, substituted $\text{C}_{(1-30)}\text{alkyl}$, or substituted $\text{C}_{(2-30)}\text{alkenyl}$;

[016] each of A^2 , A^3 , and A^4 is, independently for each occurrence, CR^6R^7 , O, S, $(\text{CH}_2)_t$ or absent;

[017] each of R^6 and R^7 , independently for each occurrence, H, F, Br, Cl, I, $\text{C}_{(1-30)}\text{alkyl}$, $\text{C}_{(2-30)}\text{alkenyl}$, substituted $\text{C}_{(1-30)}\text{alkyl}$, substituted $\text{C}_{(2-30)}\text{alkenyl}$, SR^3 , $\text{S}(\text{O})\text{R}^4$, or $\text{S}(\text{O})_2\text{R}^5$;

[018] or R^6 and R^7 together may form a ring system;

[019] m is, independently for each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

[020] n is, independently for each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

[021] p is, independently for each occurrence, 0, 1, or 2;

[022] s is, independently for each occurrence, 1, 2, 3, 4, or 5;

[023] t is, independently for each occurrence, 0, 1, 2, or 3;

[024] Z is a ligand of a biological receptor, an analog thereof, or a derivative of said ligand or of said analog;

[025] provided that:

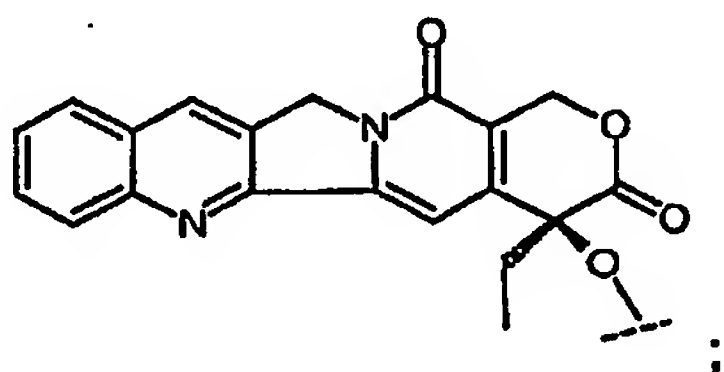
[026] when X is doxorubicin or a doxorubicin derivative, at least one of m and n is not 0; and

[027] when X is paclitaxel or a paclitaxel derivative, then B¹ is (amino acid)_p and p is 1 or 2;

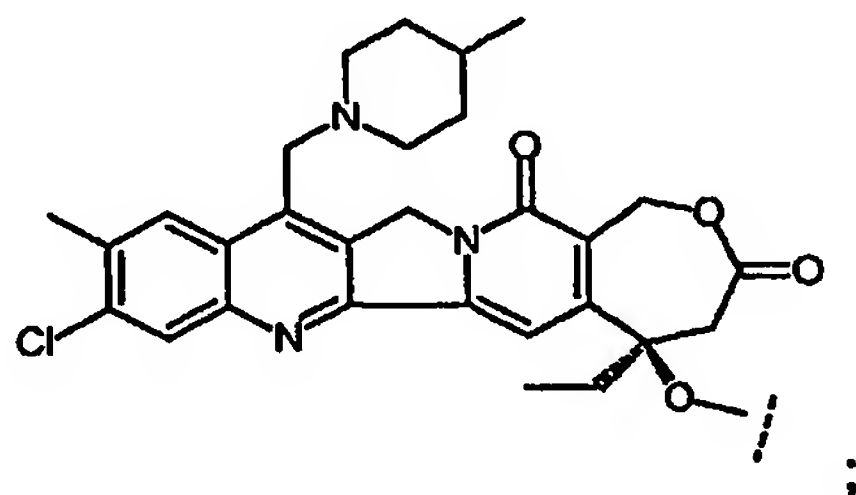
[028] A first preferred embodiment features a compound according to formula (I) wherein X is a cytotoxic moiety. More preferably X is an anthracycline. More preferably still X is camptothecin, a camptothecin derivative, paclitaxel, a paclitaxel derivative, doxorubicin, or a doxorubicin derivative; provided that: when X is doxorubicin or a doxorubicin derivative, at least one of m and n is not 0, and when X is paclitaxel or a paclitaxel derivative, then B¹ is (amino acid)_p and p is 1 or 2;

[029] In a further preferred embodiment of said first preferred embodiment said the invention features compounds of formula (I) wherein:

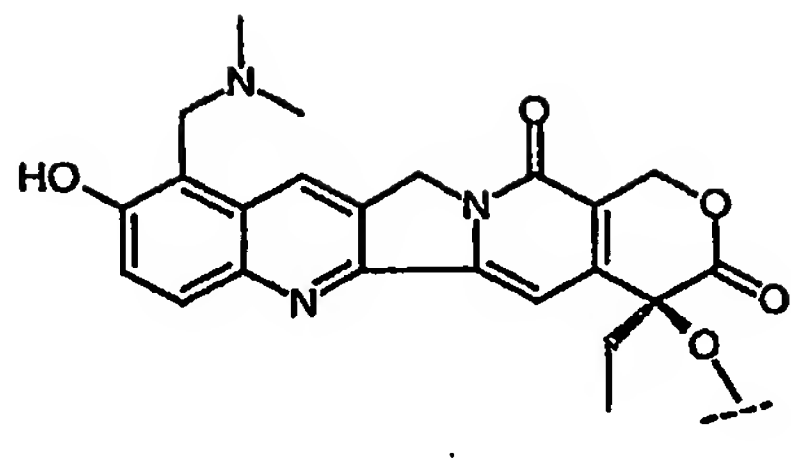
[030] X is camptothecin or a camptothecin derivative, wherein said camptothecin derivative is:



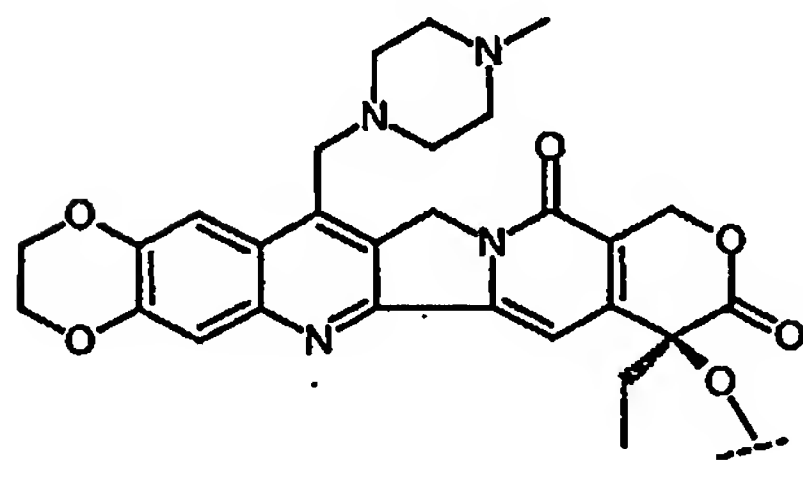
[031]



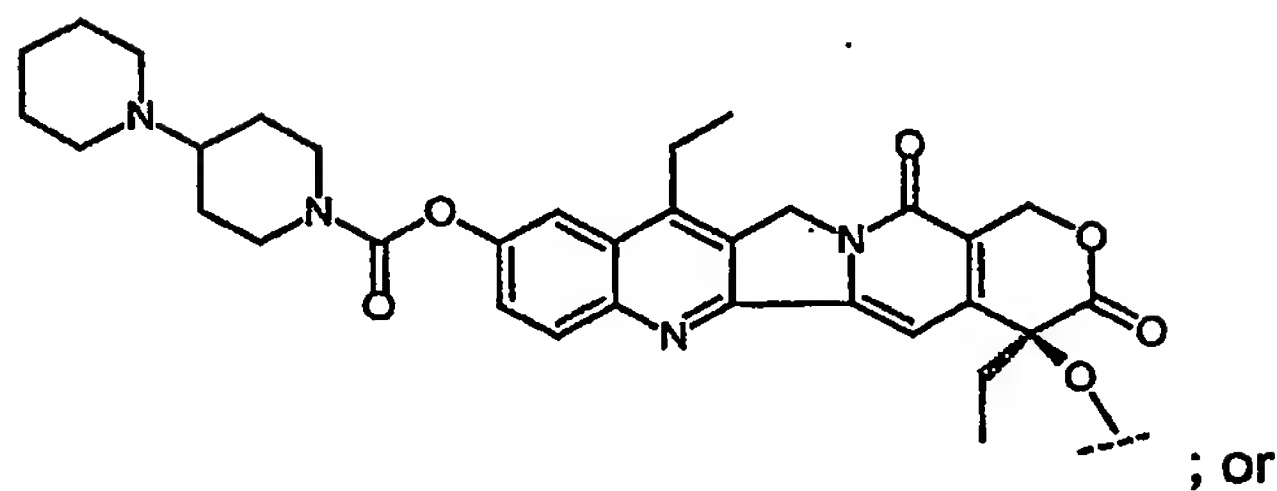
[032]



[033]

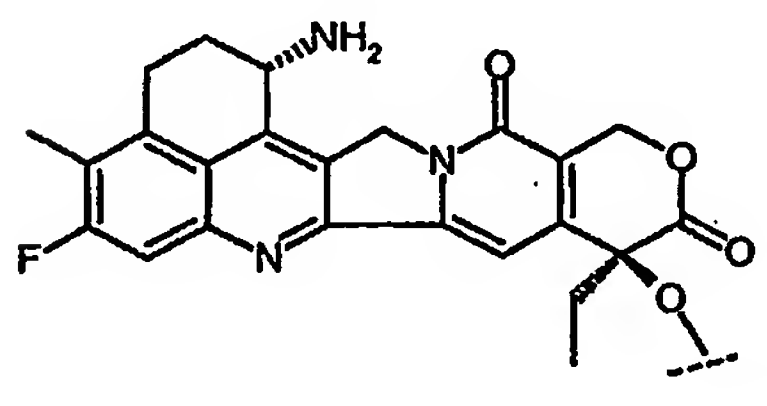


[034]



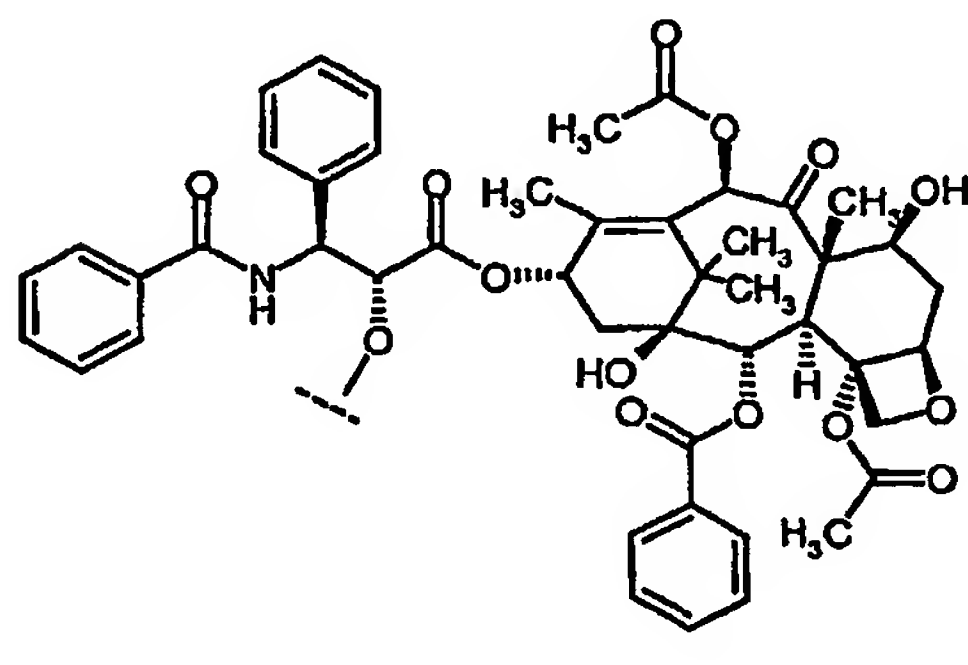
[035]

; or



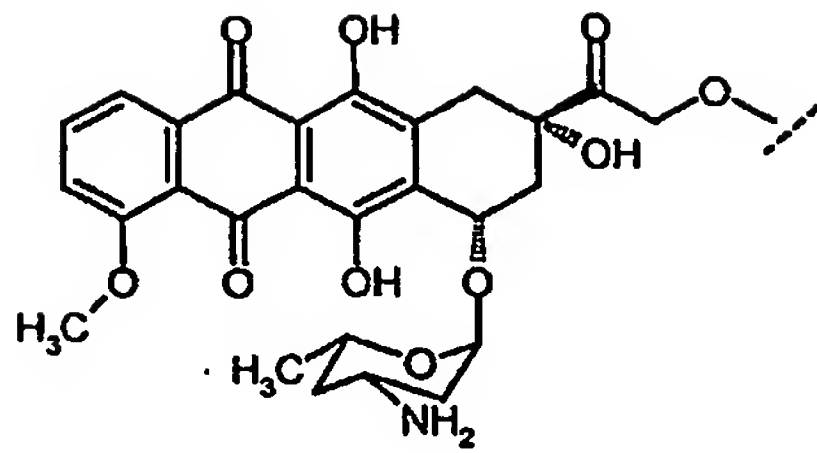
[036]

[037] or X is paclitaxel or a paclitaxel derivative, wherein said paclitaxel derivative is:



[038]

[039] or X is doxorubicin or a doxorubicin derivative, wherein said doxorubicin derivative is:



[040]

[041] A second preferred embodiment features a compound according to formula (I) wherein the ligand of Z is a somatostatin, a bombesin, or an LHRH, or an analog thereof, or a derivative of said ligand or of said analog.

[042] In a further preferred embodiment of said second preferred embodiment the invention features compounds of formula (I) wherein Z is:

[043] a somatostatin analog according to the formula:

[044] -DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;

[045] -DPhe-cyclo(Cys-3ITyr-DTrp-Lys-Val-Cys)-Thr-NH₂;

[046] -DPhe-cyclo(Cys-3ITyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;

[047] -DPhe-cyclo(Cys-3ITyr-DTrp-Lys-Thr-Cys)-Thr-NH₂;

[048] -Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;

[049] -Caeg-cyclo(DCys-Pal-DTrp-Lys-DCys)-Thr(Bzl)-Tyr-NH₂;

[050] -D2Nal-cyclo[Cys-Tyr-DTrp-Lys-Val-Cys]-Thr-NH₂;

[051] -DPhe-cyclo[Cys-Phe-DTrp-Lys-Thr-Cys]-Thr-ol;

[052] cyclo({4-(-NH-C₂H₄-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4-Bzl)-Phe); or

[053] -DPhe-cyclo[Cys-Tyr-DTrp-Lys-Val-Cys]-Trp-NH₂;

[054] or an LHRH analog according to the formula:

[055] -Glp-His-Trp-Ser-Tyr-DLys(-)-Leu-Arg-Pro-Gly-NH₂;

[056] -Glp-His-Trp-Ser-Tyr-DOrn(-)-Leu-Arg-Pro-Gly-NH₂;

[057] -Glp-His-Trp-Ser-Tyr-DDab(-)-Leu-Arg-Pro-Gly-NH₂;

[058] -Glp-His-Trp-Ser-Tyr-DDap(-)-Leu-Arg-Pro-Gly-NH₂;

[059] -Glp-His-Trp-Ser-Tyr-DApa(-)-Leu-Arg-Pro-Gly-NH₂;

- [060] -Glp-His-Trp-Ser-Tyr-DLys(-)-Leu-Arg-Pro-NHEt;
- [061] -Glp-His-Trp-Ser-Tyr-DOrn(-)-Leu-Arg-Pro-NHEt;
- [062] -Glp-His-Trp-Ser-Tyr-DDab(-)-Leu-Arg-Pro-NHEt;
- [063] -Glp-His-Trp-Ser-Tyr-DDap(-)-Leu-Arg-Pro-NHEt;
- [064] -Glp-His-Trp-Ser-His-DLys(-)-Trp-Tyr-Pro-Gly-NH₂;
- [065] -Glp-His-Trp-Ser-His-DOrn(-)-Trp-Tyr-Pro-Gly-NH₂;
- [066] -Glp-His-Trp-Ser-His-DDab(-)-Trp-Tyr-Pro-Gly-NH₂; or
- [067] -Glp-His-Trp-Ser-His-DDap(-)-Trp-Tyr-Pro-Gly-NH₂;
- [068] or a bombesin analog according to the formula:
- [069] -Gln-Trp-Ala-Val-Gly-His-Leu-Ψ(CH₂;-NH)-Leu-NH₂;
- [070] -Gln-Trp-Ala-Val-Gly-His-Leu-Ψ(CH₂;-NH)-Phe-NH₂;
- [071] -Gln-Trp-Ala-Val-βAla-His-Leu-Leu-NH₂;
- [072] -Gln-Trp-Ala-Val-βAla-His-Leu-Nle-NH₂;
- [073] -Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH₂;
- [074] -Gln-Trp-Ala-Val-Gly-His-Phe-Met-NH₂;
- [075] -Gln-Trp-Ala-Val-βAla -His-Phe-Nle-NH₂;
- [076] -Gln-Trp-Ala-Ala-βAla -His-Phe-Nle-NH₂;
- [077] -Gln-Trp-Ala-Val-βAla -His-Ala-Nle-NH₂;
- [078] -Gln-Trp-Ala-Val-βAla -Ala-Phe-Nle-NH₂;
- [079] -Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH₂;
- [080] -DPhe-Gln-Trp-Ala-Val-Gly-His-Leu-Ψ(CH₂;-NH)-Leu-NH₂;
- [081] -DPhe-Gln-Trp-Ala-Val-Gly-His-Leu-Ψ(CH₂;-NH)-Phe-NH₂;
- [082] -DPhe-Gln-Trp-Ala-Val-βAla-His-Leu-Leu-NH₂;
- [083] -DPhe-Gln-Trp-Ala-Val-βAla-His-Leu-Nle-NH₂;
- [084] -DPhe-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH₂;
- [085] -DPhe-Gln-Trp-Ala-Val-Gly-His-Phe-Met-NH₂;

- [086] -DAla-Gln-Trp-Ala-Val-βAla -His-Phe-Nle-NH₂;
- [087] -DPhe-Gln-Trp-Ala-Val-βAla -His-Phe-Nle-NH₂;
- [088] -DPhe-Gln-Trp-Ala-Ala-βAla -His-Phe-Nle-NH₂;
- [089] -DPhe-Gln-Trp-Ala-Val-βAla -His-Ala-Nle-NH₂;
- [090] -DPhe-Gln-Trp-Ala-Val-βAla -Ala-Phe-Nle-NH₂; or
- [091] -DPhe-Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH₂.

[092] A third preferred embodiment features a compound according to formula (I) wherein at least one of m and n is not 0.

[093] A fourth preferred embodiment features a compound the structure of which is specifically disclosed herein. More preferred are compounds and intermediates described in examples 1-75 herein. More preferred still are compounds of examples 19-25, 28-32, 40-42, 45-65, and 74-75.

[094] In a fifth preferred embodiment is featured a compound selected from the compounds listed in Appendix A.

[095] In a sixth preferred embodiment is featured a compound selected from the compounds listed in Appendix B.

[096] In a seventh preferred embodiment is featured a compound selected from the compounds listed in Appendix C.

[097] In an eighth preferred embodiment is featured a compound selected from the compounds listed in Appendix D.

[098] In a ninth preferred embodiment is featured a compound selected from the compounds listed in Appendix E.

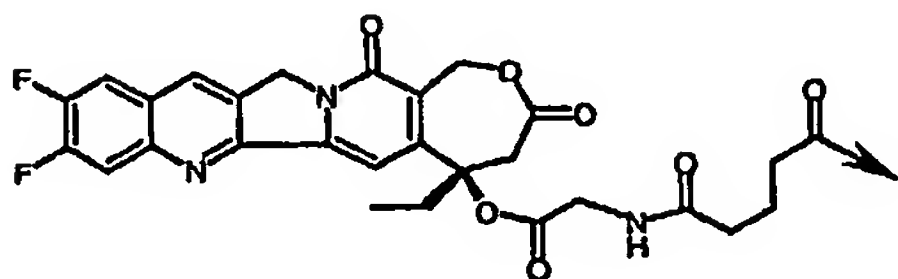
[099] In a tenth preferred embodiment is featured a compound selected from the compounds listed in Appendix F.

[0100] In a eleventh preferred embodiment is featured a compound selected from the compounds listed in Appendix G.

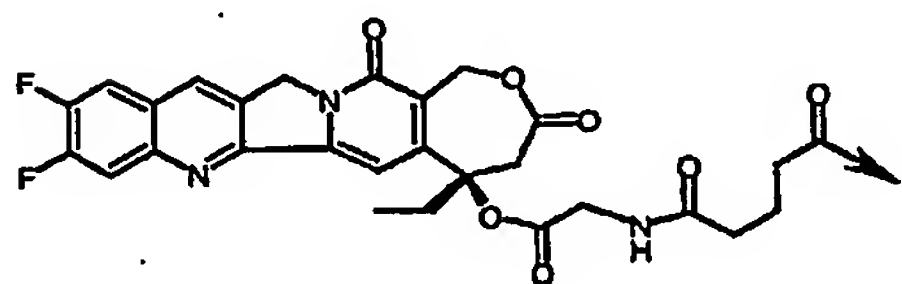
[0101] In a twelfth preferred embodiment is featured a compound selected from the compounds listed in Appendix H.

[0102] In a thirteenth preferred embodiment is featured a compound selected from the compounds listed in Appendix I.

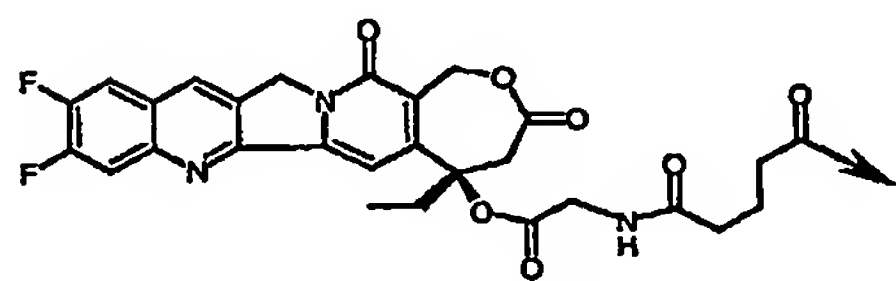
[0103] In a fourteenth preferred embodiment is featured a compound according to the formula:



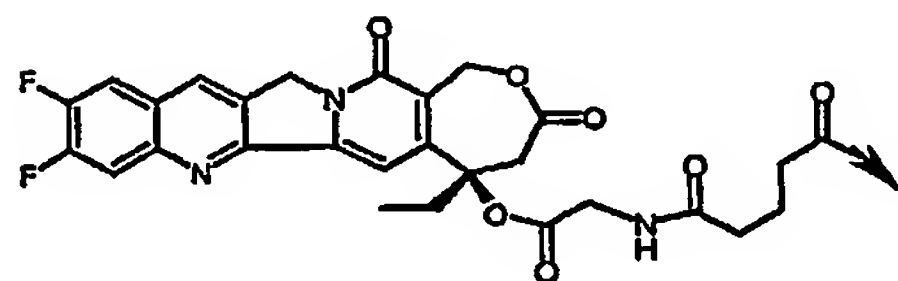
[0104] - (Doc)₄-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;



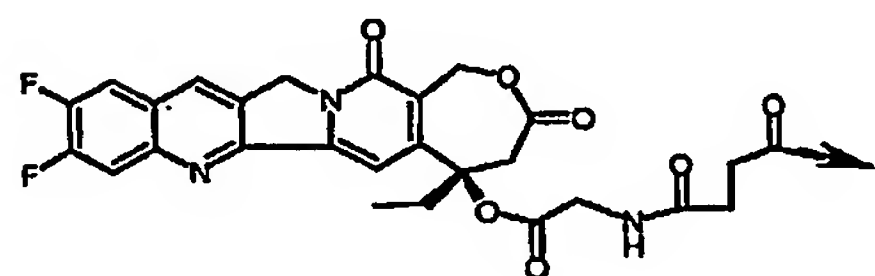
[0105] --(Doc)₆-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;



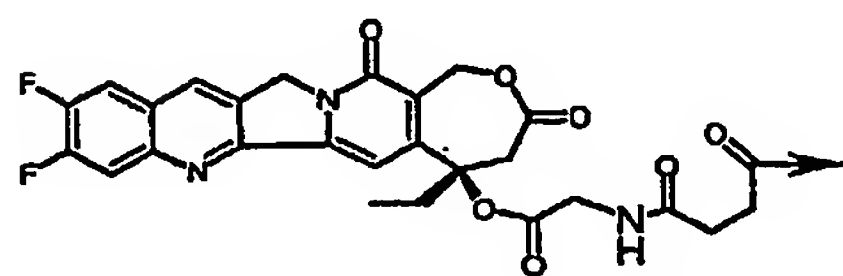
[0106] --Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;



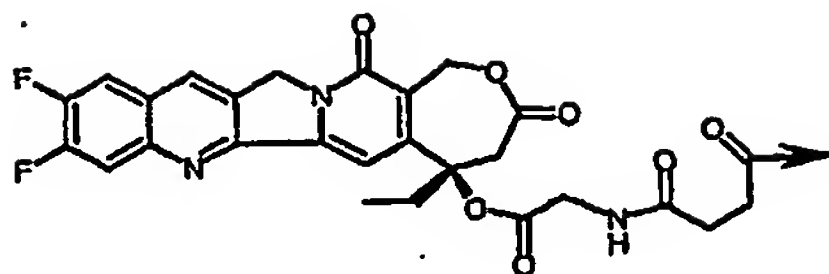
[0107] --Aepa-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂ ;



[0108] --(Doc)₄-Aepa-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;

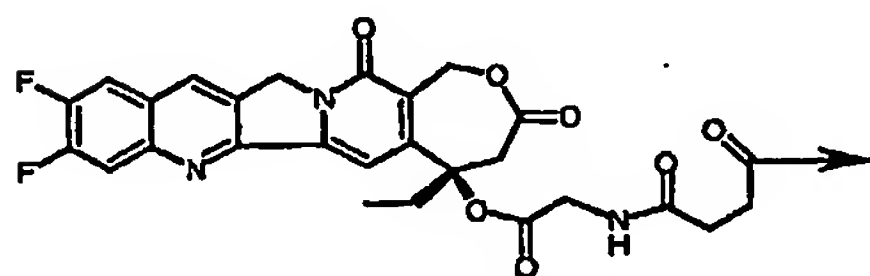


[0109] --(Doc)₄-Aepa-DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;



[0110]

--DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂; or



[0111]

--Aepa-DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;

[0112] or a pharmaceutically acceptable salt thereof.

[0113] As used herein the term "amino acid" refers to any naturally occurring and unnatural amino acids, including but not limited to α -amino acids, β -amino acids, γ -amino acids, and may be either D-amino acids or L-amino acids unless otherwise indicated. With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala) of amino acids in this disclosure stand for the structure of -NH-C(R)(R')-CO-, wherein R and R' each is, independently, hydrogen or the side chain of an amino acid (e.g., R = CH₃ and R' = H for Ala), or R and R' may be joined to form a ring system. For the N-terminal amino acid, the abbreviation stands for the structure of (R²R³)-N-C(R)(R')-CO-, wherein R² and R³ are as defined in formula (I).

[0114] An exemplary list of preferred amino acids includes, but is not limited to, Ala, Arg, Asp, Asn, Cys, Glu, Gln, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, Val, β -Ala, Act, Apc, Gaba, Apn, Ahx, Ahp, Aoc, Anc, Adc, Aun, Ado, Acc, A3c, A4c, A5c, A6c, Aib, Orn, Dab, Dap, hArg, 4Pal, 3Pal, 2Pal, Abu, Cha, Cit, Nle, Nva, Taz, 2Thi, 3Thi, Dhp, Dmt, 2Fua, 3Hyp, 4Hyp, Inc, Inp, Ktp, hLeu, Oic, hPhe, Pip, Sar, Thz, Tic, Tle, Phg and Caeg.

[0115] The peptide portion of compounds of the invention may also be denoted herein by another format, e.g., (Tyr¹¹)Somatostatin(1-14)-NH₂, with the substituted amino acid(s) from the natural sequence placed between the first set of parentheses (e.g., Tyr¹¹ for Phe¹¹ in somatostatin). The numbers between the second set of parentheses refer to the number of amino acids present in the peptide (e.g., somatostatin(1-11) refers to amino acids 1 through 11 of the peptide sequence for somatostatin). The designation "NH₂" in e.g., (Tyr¹¹)Somatostatin(1-14)-NH₂, indicates that the C-terminus of the peptide is amidated. (Tyr¹¹)Somatostatin(1-14), or alternatively (Tyr¹¹)Somatostatin(1-14)-OH, indicates that the C-terminus is the free acid.

[0116] "Alkyl" refers to a hydrocarbon group containing one or more carbon atoms, where multiple carbon atoms if present are joined by single bonds. The alkyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups.

[0117] "Substituted alkyl" refers to an alkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH₂, -NHCH₃, -NO₂, -C₁₋₂ alkyl substituted with 1 to 6 halogens, -CF₃, -OCH₃, -OCF₃, and -(CH₂)₀₋₄-COOH. In different embodiments 1, 2, 3 or 4 substituents are present. The presence of -(CH₂)₀₋₄-COOH results in the production of an alkyl acid. Examples of alkyl acids containing, or consisting of, -(CH₂)₀₋₄-COOH include 2-norbornane acetic acid, tert-butyric acid and 3-cyclopentyl propionic acid.

[0118] "Heteroalkyl" refers to an alkyl wherein one or more of the carbon atoms in the hydrocarbon group are replaced with one or more of the following groups: amino, amido, -O-, or carbonyl. In different embodiments 1 or 2 heteroatoms are present.

[0119] "Substituted heteroalkyl" refers to a heteroalkyl wherein one or more hydrogen atoms of the hydrocarbon group are replaced with one or more substituents selected from the group consisting of halogen, (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH₂, -NHCH₃, -NO₂, -C₁₋₂ alkyl substituted with 1 to 6 halogens, -CF₃, -OCH₃, -OCF₃, and -(CH₂)₀₋₄-COOH. In different embodiments 1, 2, 3 or 4 substituents are present.

[0120] "Alkenyl" refers to a hydrocarbon group made up of two or more carbons where one or more carbon-carbon double bonds are present. The alkenyl hydrocarbon group may be straight-chain or contain one or more branches or cyclic groups.

[0121] "Substituted alkenyl" refers to an alkenyl wherein one or more hydrogens are replaced with one or more substituents selected from the group consisting of halogen (i.e., fluorine, chlorine, bromine, and iodine), -OH, -CN, -SH, -NH₂, -NHCH₃, -NO₂, -C₁₋₂ alkyl substituted with 1 to 6 halogens, -CF₃, -OCH₃, -OCF₃, and -(CH₂)₀₋₄-COOH. In different embodiments 1, 2, 3 or 4 substituents are present.

[0122] "Aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups. Preferably, the aryl is a 5 or 6 membered ring. Preferred atoms for a heterocyclic aryl are one or more sulfur, oxygen, and/or nitrogen. Examples of aryl include phenyl, 1-naphthyl, 2-naphthyl, indole, quinoline, 2-imidazole,

and 9-anthracene. Aryl substituents are selected from the group consisting of $-C_{1-4}$ alkyl, $-C_{1-4}$ alkoxy, halogen (i.e., fluorine, chlorine, bromine, and iodine), $-OH$, $-CN$, $-SH$, $-NH_2$, $-NO_2$, $-C_{1-2}$ alkyl substituted with 1 to 5 halogens, $-CF_3$, $-OCF_3$, and $-(CH_2)_{0-4}-COOH$. In different embodiments the aryl contains 0, 1, 2, 3, or 4 substituents.

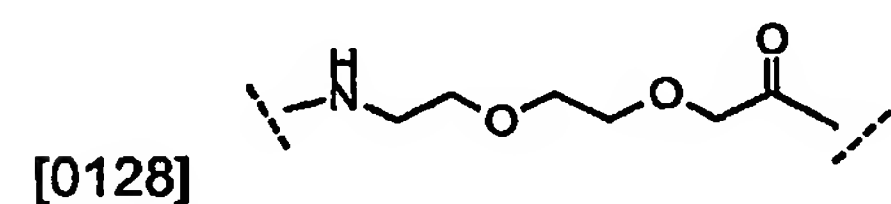
[0123] "Alkylaryl" refers to an "alkyl" joined to an "aryl".

[0124] The term cycloalkyl is intended to include a mono-cycloalkyl group or a bi-cycloalkyl group of the indicated carbon number known to those of skill in the art.

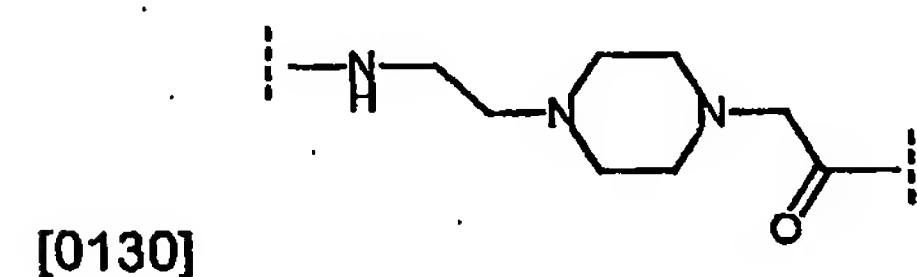
[0125] The term heterocycle includes mono-cyclic and bi-cyclic systems having one or more heteroatoms, such as oxygen, nitrogen and/or sulfur. The ring systems may be aromatic, for example pyridine, indole, quinoline, pyrimidine, thiophene (also known as thienyl), furan, benzothiophene, tetrazole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, and thiadiazole. The ring systems also may be non-aromatic, for example pyrrolidine, piperidine, morpholine and the like.

[0126] The chemist of ordinary skill will recognize that certain combinations of heteroatom-containing substituents listed in this invention define compounds which will be less stable under physiological conditions. Accordingly, such compounds are less preferred.

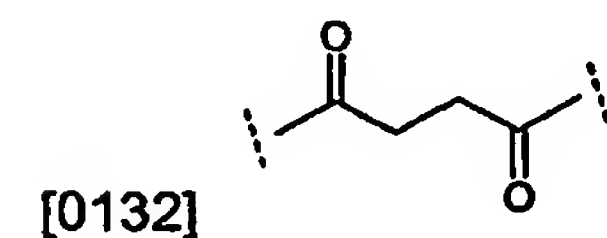
[0127] Doc is 8-amino-3,6-dioxaoctanoic acid, represented by the structure:



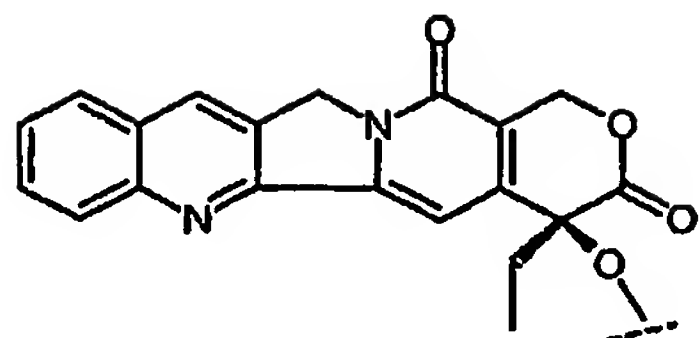
[0129] Aepa is 4-(2-aminoethyl)-1-carboxy methyl-piperazine, represented by the structure:



[0131] Suc is succinyl, represented by the structure:

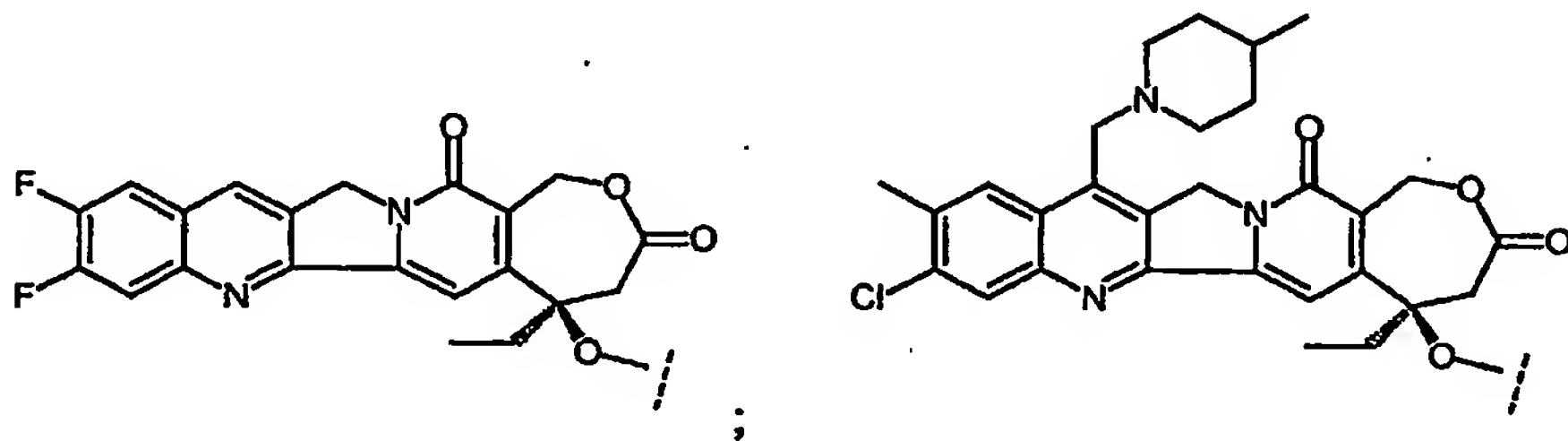


[0133] Camptothecin moiety:

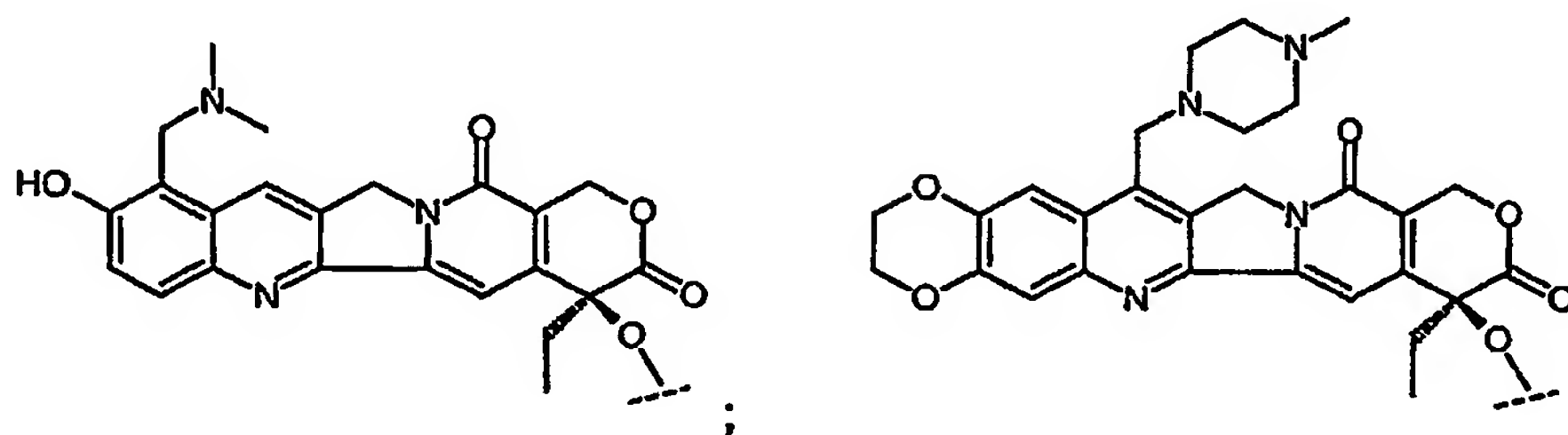


[0134]

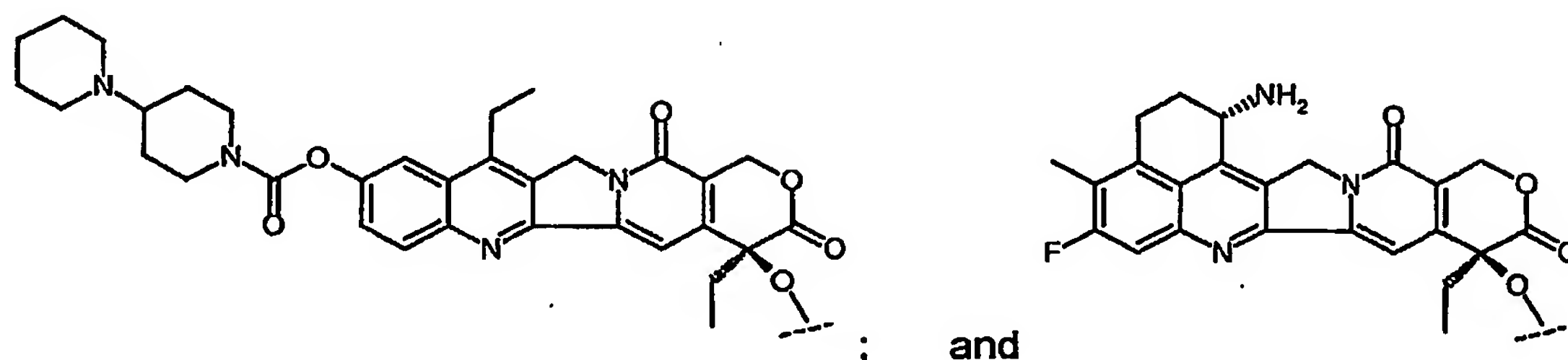
[0135] Camptothecin derivative moieties include but are not limited to:



[0136]



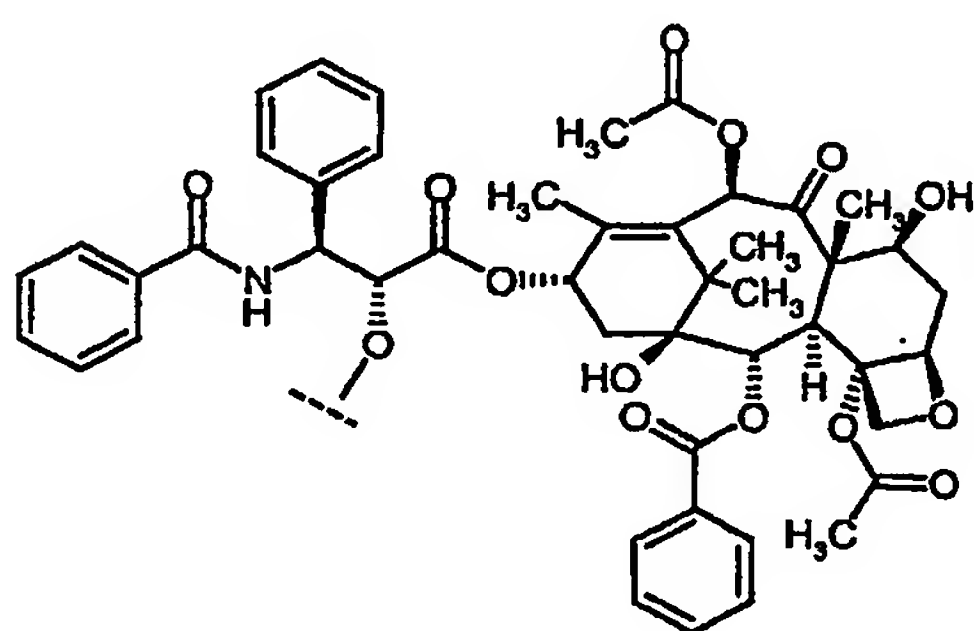
[0137]



[0138]

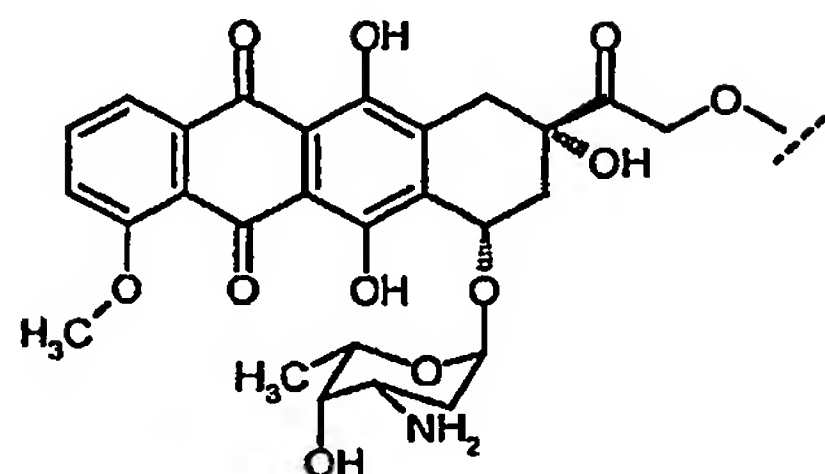
and

[0139] Paclitaxel moiety:



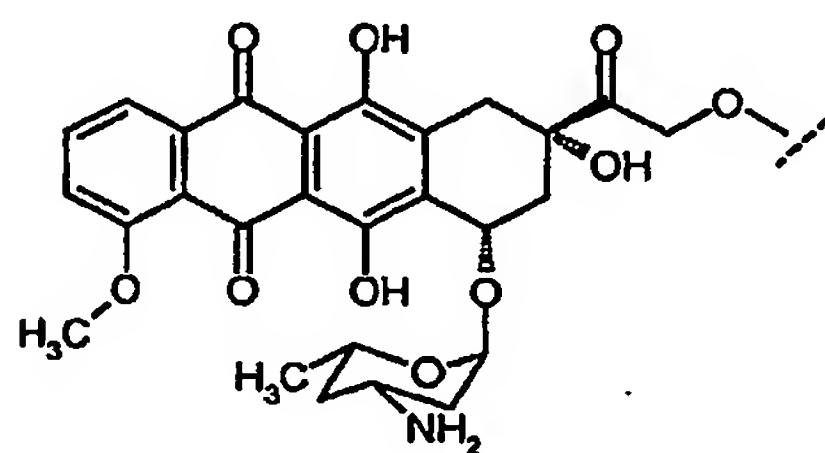
[0140]

[0141] Doxorubicin moiety:



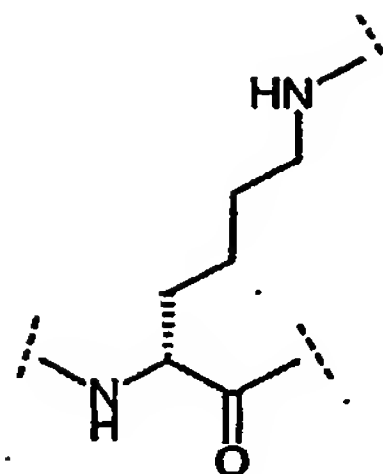
[0142]

[0143] Doxorubicin derivative moieties include but are not limited to:

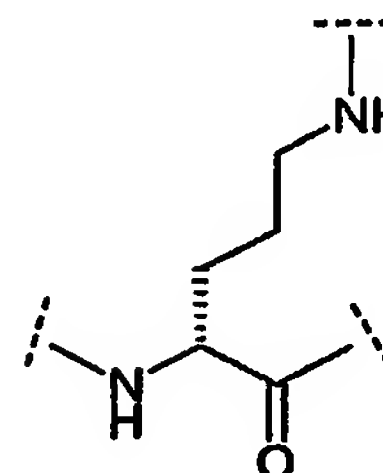


[0144]

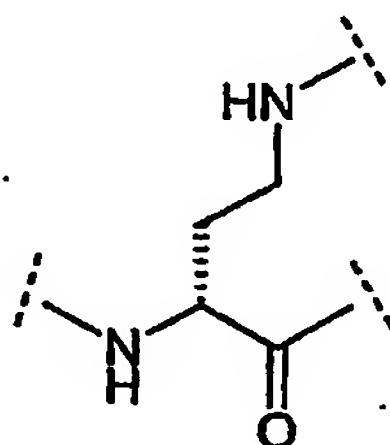
[0145] DLys(-) is represented by the structure:

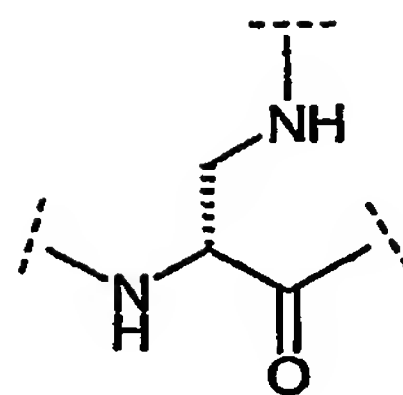


[0146] DOrn(-) is represented by the structure:

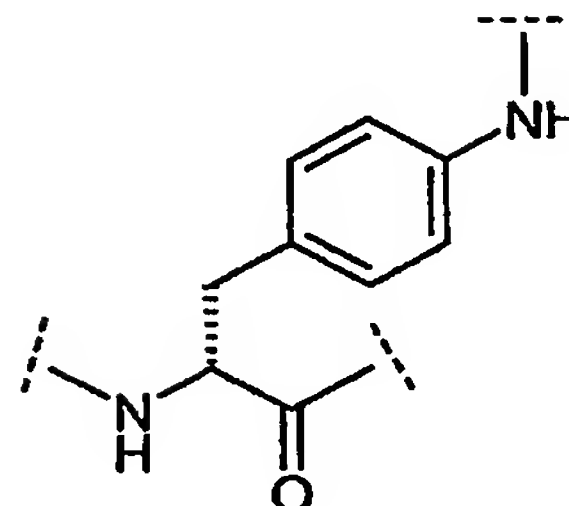


[0147] DDab(-) is represented:





[0148] DAp(-) is represented by the structure:



[0149] DApa(-) is represented by the structure:

[0150] Abu α -aminobutyric acid

[0151] Acc 1-amino-1-cyclo(C₃-C₉)alkyl carboxylic acid

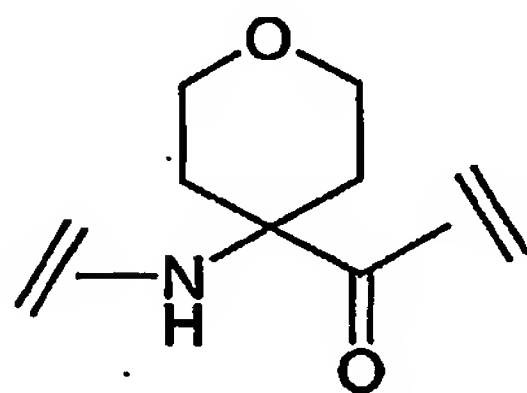
[0152] A3c 1-amino-1-cyclopropanecarboxylic acid

[0153] A4c 1-amino-1-cyclobutanecarboxylic acid

[0154] A5c 1-amino-1-cyclopentanecarboxylic acid

[0155] A6c 1-amino-1-cyclohexanecarboxylic acid

[0156] Act 4-amino-4-carboxytetrahydropyran, represented by the structure:

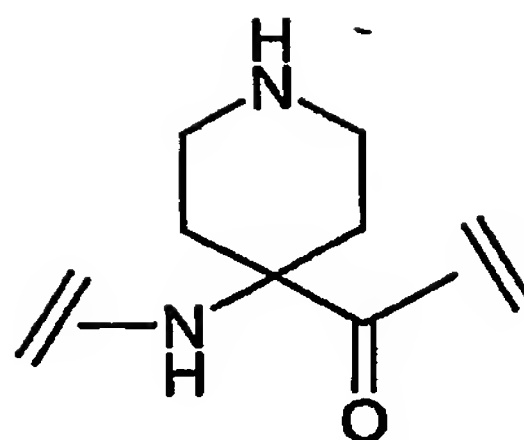


[0157]

[0158] Aib α -aminoisobutyric acid

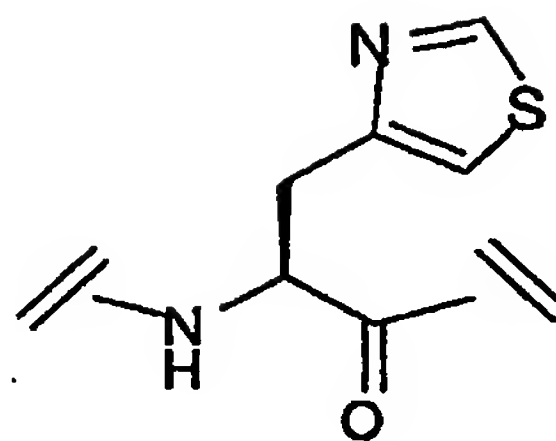
[0159] Ala or A alanine

[0160] β -Ala beta-alanine



[0161] Apc	denotes the structure:
[0162] Arg or R	arginine
[0163] hArg	homoarginine
[0164] Asn or N	asparagine
[0165] Asp or D	aspartic acid
[0166] Cha	β -cyclohexylalanine
[0167] Cys or C	cysteine
[0168] Dab	2,4-diaminobutyric acid
[0169] Dap	2,3-diaminopropionic acid
[0170] Dhp	3,4-dehydroproline
[0171] Dmt	5,5-dimethylthiazolidine-4-carboxylic acid
[0172] 2Fua	β -(2-furyl)-alanine
[0173] Gln or Q	glutamine
[0174] Glu or E	glutamic acid
[0175] Gly or G	glycine
[0176] His or H	histidine
[0177] 3Hyp acid	trans-3-hydroxy-L-proline, i.e., (2S, 3S)-3-hydroxypyrrolidine-2-carboxylic acid
[0178] 4Hyp	4-hydroxyproline, i.e., (2S, 4R)-4-hydroxypyrrolidine-2-carboxylic acid
[0179] Ile or I	isoleucine
[0180] Inc	indoline-2-carboxylic acid
[0181] Inp	isonipecotic acid
[0182] Ktp	4-ketoproline

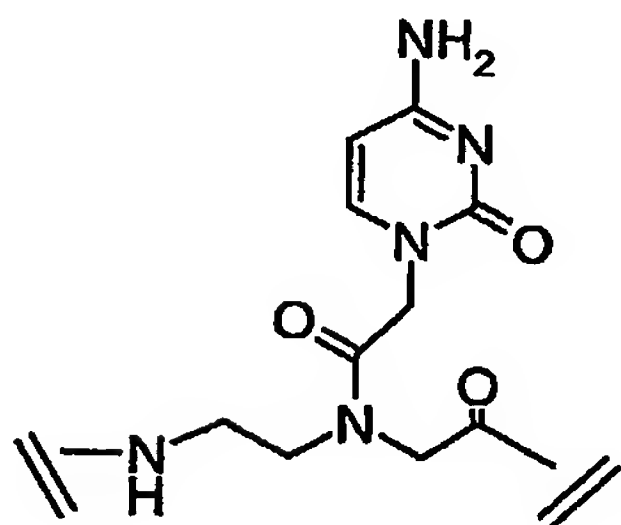
[0183] Leu or L	leucine
[0184] hLeu	homoleucine
[0185] Lys or K	lysine
[0186] Met or M	methionine
[0187] Nle	norleucine
[0188] Nva	norvaline
[0189] Oic	octahydroindole-2-carboxylic acid
[0190] Orn	ornithine
[0191] 2Pal	β -(2-pyridinyl)alanine
[0192] 3Pal	β -(3-pyridinyl)alanine
[0193] 4Pal	β -(4-pyridinyl)alanine
[0194] Phe or F	phenylalanine
[0195] hPhe	homophenylalanine
[0196] Pip	pipecolic acid
[0197] Pro or P	proline
[0198] Sar	Sarcosine
[0199] Ser or S	serine



[0200] Taz	β -(4-thiazolyl)alanine, i.e.,
[0201] 2Thi	β -(2-thienyl)alanine
[0202] 3Thi	β -(3-thienyl)alanine
[0203] Thr or T	threonine
[0204] Thz	thiazolidine-4-carboxylic acid

[0205] Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
[0206] Tle	tert-leucine
[0207] Trp or W	tryptophan
[0208] Tyr or Y	tyrosine
[0209] Val or V	valine
[0210] Gaba	4-Aminobutyric acid
[0211] Apn	5-Aminopentanoic acid
[0212] Ahx	6-Aminohexanoic acid
[0213] Ahp	7-Aminoheptanoic acid
[0214] Aoc	8-Aminooctanoic acid
[0215] Anc	9-Aminononanoic acid
[0216] Adc	10-Aminodecanoic acid
[0217] Aun	11-Aminoundecanoic acid
[0218] Ado	12-Aminododecanoic acid
[0219] Phg	Phenylglycine
[0220] Caeg	denotes the structure:

[0221]



[0222] Certain other abbreviations used herein are defined as follows:

[0223] Aloc:	Allyloxycarbonyl
[0224] Boc:	tert-butyloxycarbonyl
[0225] Bhoc	benzhydryloxycarbonyl

[0226] Bzl:	benzyl
[0227] DCM:	dichloromethane
[0228] DIC:	N, N-diisopropylcarbodiimide
[0229] DIEA:	diisopropylethyl amine
[0230] Dmab:	4-{N-(1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl)-amino}
benzyl	
[0231] DMAP:	4-(dimethylamino)pyridine
[0232] DMF	dimethylformamide
[0233] DNP:	2,4-dinitrophenyl
[0234] Fmoc:	Fluorenylmethyloxycarbonyl
[0235] HBTU:	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium
hexafluorophosphate	
[0236] cHex	cyclohexyl
[0237] HOAT:	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium
hexafluorophosphate	
[0238] HOBt:	1-hydroxy-benzotriazole
[0239] Mmt:	4-methoxytrityl
[0240] NMP:	N-methylpyrrolidone
[0241] Pbf:	2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl
[0242] tBu:	tert-butyl
[0243] TIS:	triisopropylsilane
[0244] TOS:	tosyl
[0245] trt	trityl
[0246] TFA:	trifluoro acetic acid
[0247] TFFH:	tetramethylfluoroformidinium hexafluorophosphate
[0248] Z:	benzyloxycarbonyl

[0249] Example 1

[0250] H-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin

[0251] The titled protected peptide-resin was automatically synthesized on an Applied Biosystems (ABI) (Foster City, CA) model 433A peptide synthesizer by using Fluorenylmethyloxycarbonyl (Fmoc) chemistry. A Rink Amide MBHA (4-methylbenzylhydramine) resin (Novabiochem, San Diego, CA) with substitution of 0.72 mmol/g was used. The following Fmoc amino acids (AnaSpec, San Jose, CA) were used: Fmoc-Thr(tBu)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-DTrp(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoc-DTyr(tBu)-OH, Fmoc-Phe-OH, Fmoc-Cys(Trt)-OH, Fmoc-Thr(tBu)-OH, and Fmoc-Abu-OH. The synthesis was carried out on a 0.25 mmol scale. The Fmoc groups were removed by treatment with 20% piperidine in N-methylpyrrolidone (NMP) for 30 min. In each coupling step, the Fmoc amino acid (4 eq, 1 mmol) was first pre-activated in 2 mL of a solution containing 0.45M 2-(1-H-benzotriazole-1-yl)-1,1,2,3-tetramethyluronium hexafluorophosphate (HBTU) and 0.45M 1-hydroxy-benzotriazole (HOBT) in *N,N*-dimethylformamide (DMF). The resulting activated amino acid ester, 1 mL of diisopropylethylamine (DIEA) and 1 mL of NMP were added to the resin. The ABI 433A peptide synthesizer was programmed to perform the following reaction cycle: (1) washing with NMP, (2) removing Fmoc protecting group with 20% piperidine in NMP for 30 min, (3) washing with NMP, (4) coupling with pre-activated Fmoc amino acid for 1h. The resin was coupled successively according to the sequence. After peptide chain was assembled, the Fmoc was removed and the resin was washed completely by using DMF and dichloromethane (DCM).

[0252] Example 2

[0253] H-Doc-Doc-Doc-Doc-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin

[0254] The titled protected peptide-resin was synthesized substantially according to the procedure described in Example 1. Fmoc-8-amino-3, 6-dioxaoctanoic acid (Fmoc-Doc-OH) was purchased from Chem-Impex International, Wood Dale, IL. After the assembly of H-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin (0.45 mmol scale), the protected peptide-resin was transferred into a reaction vessel on a shaker for manual synthesis. The resin was shaken with a DMF solution of Fmoc-Doc-OH (1.5 eq, 0.75 mmol), *N,N*-diisopropylcarbodiimide (DIC, 1.5 eq, 0.75 mmol) and HOBT (1.5 eq, 0.75 mmol) for 2 h. The resin was washed with DMF and treated with 20% piperidine in DMF to remove Fmoc protecting group. The rest of the three Doc residues were sequentially

coupled to the resin using the same manual operation procedure. After removing Fmoc protecting group with 20% piperidine in DMF, the protected peptide-resin was washed with DMF and DCM.

[0255] Example 3

[0256] H-Doc-Doc-Doc-Doc-Doc-Doc-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin

[0257] The titled protected peptide-resin was synthesized substantially according to the procedure described in Example 2.

[0258] Example 4

[0259] H-Aepa-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin

[0260] The titled protected peptide-resin was synthesized substantially according to the procedure described in Example 1. Fmoc-4-(2-aminoethyl)-1-carboxymethyl-piperazine (Fmoc-Aepa-OH) was purchased from Neosystem, Strasbourg, France. After the assembly of H-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin, the protected peptide-resin was transferred into a reaction vessel on a shaker for manual synthesis. The Fmoc-Aepa-OH (1.5 eq, 0.75 mmol) was pre-activated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 1.4 eq, 0.7 mmol) and 1-hydroxy-7-azabenzotriazole (HOAT, 1.4 eq., 0.7 mmol) in 2 mL of DMF for 2 min. The resulting activated ester of Fmoc-Aepa-OH and 1 mL of DIEA were added into the reaction vessel and the mixture was shaken for 2h. The resin was washed with DMF and treated with 20% piperidine in DMF to remove Fmoc protecting group. The protected peptide-resin was washed with DMF and DCM.

[0261] Example 5

[0262] H-Doc-Doc-Doc-Doc-Aepa-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin

[0263] The titled protected peptide-resin was synthesized substantially according to the procedure described in Example 4. The couplings of Fmoc-Doc-OH were performed according to the corresponding procedure described in Example 2.

[0264] Example 6

[0265] H-DPhe-Cys(Trt)-Tyr(tBu)-DTTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin

[0266] The titled protected peptide-resin was synthesized substantially according to the procedure described in Example 1. Fmoc-DPhe-OH was purchased from AnaSpec, San Jose, CA.

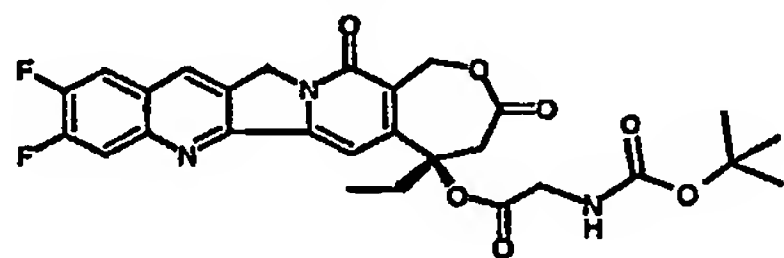
[0267] Example 7

[0268] H-Aepa-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin

[0269] The titled protected peptide-resin was synthesized substantially according to the procedure described in Example 4.

[0270] Example 8

[0271] 5-O-tBoc-glycyl-5-(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione:

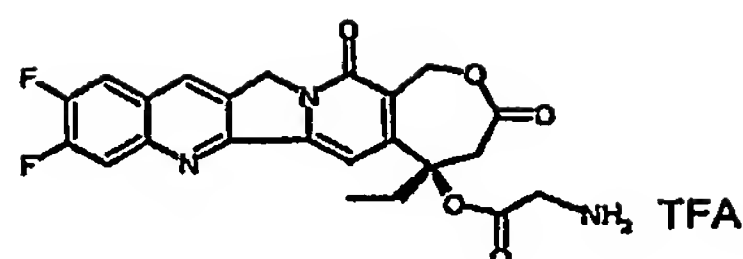


[0272]

[0273] 5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-5-hydroxy-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione (300 mg), Boc-Gly-OH (923 mg, 7eq.) and 4-(dimethylamino)pyridine (DMAP) (560.4 mg, 6 eq.) were dissolved in a mixed solvent system of DCM and DMF (30 mL, v/v, 30/0.5). To the solution was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.08 g, 7.5 eq.). The mixture was stirred overnight at room temperature and the solvents were removed under reduced pressure. The residue was dissolved in 100 mL of DCM and washed successively with 10% citric acid aqueous solution (20 mL x 2), saturated NaHCO₃ (20 mL x 2) and brine (10 mL x 3). The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure. The crude product was purified by a flash chromatography on a silica gel column using 10% methanol in DCM as the eluent to give a pure product of 5-O-tBoc-glycyl-5-(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione. 330 mg, TLC (silica gel, DCM/MeOH: 9/1): R_f=0.43. Electro-spray ionization mass spectrometry (ESI MS) analysis gave the molecular weight at 556.4 (in agreement with the calculated molecular weight of 555.5).

[0274] Example 9

[0275] 5-O-glycyl-5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione TFA salt



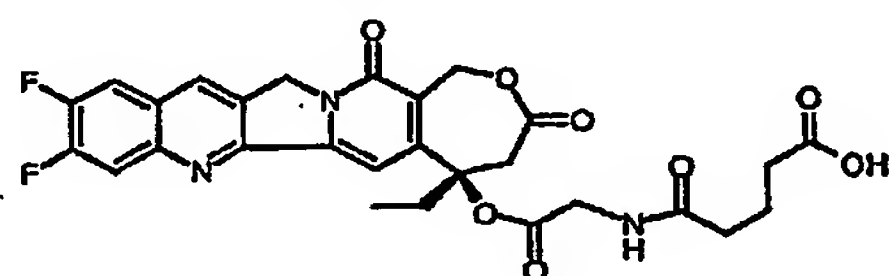
[0276]

[0277] 5-O-(tBoc-glycyl-5-(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-

oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione (330 mg) was treated with 30% trifluoroacetic acid (TFA) solution in DCM under nitrogen for 1h. TFA and solvent were removed under reduced pressure. The residue was triturated with cold ether to give a light yellow powder. TLC (silica gel, DCM/MeOH: 9/1): R_f =0.13. ESI MS analysis gave the molecular weight at 456.0 (in agreement with the calculated molecular weight of 455.4).

[0278] Example 10

[0279] 5-O-(N-glutaryl-glycyl)-5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione

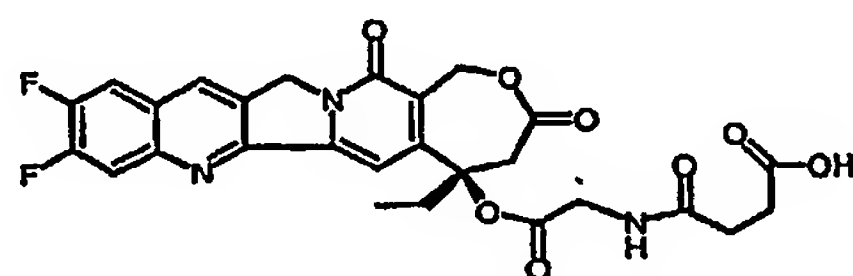


[0280]

[0281] A mixture of 5-O-glycyl-5-(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione (208 mg, 0.37 mmol), glutaric anhydride (66 mg, 0.58 mmol, 1.5 eq.) and triethylamine (243 mL) in DMF (7 mL) was stirred at room temperature for 3h. The solvent was removed under reduced pressure. The residue was dissolved in water (10 mL) and the pH of the solution was adjusted to 3 by adding 0.5N HCl solution at 0 °C. The precipitate formed was collected by filtration and washed with cold water and ether. After drying under reduced pressure, a solid was obtained (160 mg). Yield was 77%. ESI MS analysis gave the molecular weight at 570.0 (in agreement with the calculated molecular weight of 569.5). Purity was 98% based on analytical HPLC analysis.

[0282] Example 11

[0283] 5-O-(N-succinyl-glycyl)-5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione



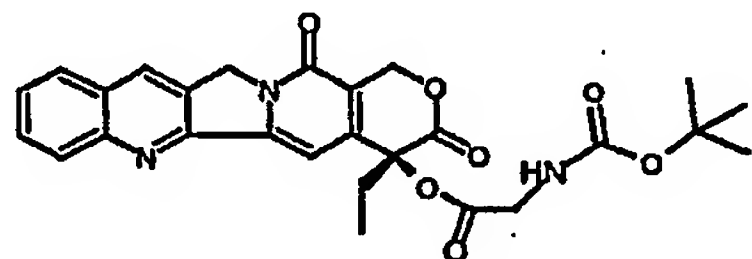
[0284]

[0285] The titled compound was synthesized substantially according to the procedure described in Example 10 by using succinic anhydride. The yield was 86%. ESI MS analysis gave the

molecular weight at 556.2 (in agreement with the calculated molecular weight of 555.50). Purity was 96% based on the analytical HPLC analysis.

[0286] Example 12

[0287] Camptothecin-20-(S)-[O-(tBoc-glycyl)]

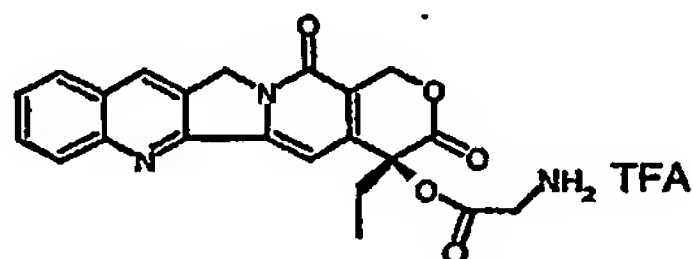


[0288]

[0289] Camptothecin (0.79 g, 2.2 mmol), Boc-Gly-OH (1.2 g, 6.8 mmol, 3 eq.) and DMAP (0.83 g, 6.8 mmol, 3 eq.) were dissolved in a mixed solvent system of DCM and THF (18 mL, v/v, 5/1). The mixture was cooled in an ice-water bath. To it was added 1,3-diisopropylcarbodiimide (DIC) (1.1 mL, 6.8 mmol, 3.1 eq.). After stirring at 0 °C for 0.5h, the mixture was warmed to room temperature and stirred overnight. The solution was diluted with 50 mL of DCM and washed successively with 10% citric acid aqueous solution (20 mL x 2), saturated NaHCO₃ (20 mL x 2) and brine (10 mL x 3). The organic layer was dried over MgSO₄, filtered and evaporated under reduced pressure to dryness. The crude product was purified by a flash chromatography on a silica gel column using 4% methanol in DCM as the eluent to give a pure product of camptothecin-20-(S)-[O-(tBoc-glycyl)] (1.07 g, white solid). TLC (silica, DCM/MeOH: 9/1): R_f=0.6. MS ESI analysis gave the molecular weight at 506.3 (in agreement with the calculated molecular weight of 505.53).

[0290] Example 13

[0291] Camptothecin-20-(S)-[O-(glycyl)] TFA salt

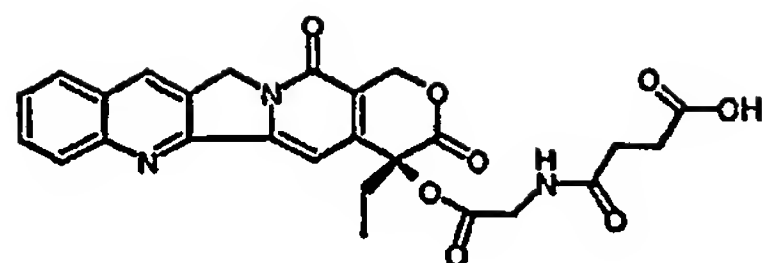


[0292]

[0293] Camptothecin-20-(S)-[O-(Boc-glycyl)] (1.07g, 2.1 mmol) was treated with 50% TFA in DCM under N₂ for 1h. TFA and the solvent were removed under reduced pressure. The residue was triturated with cold ether. The precipitate formed was collected by filtration and washed with cold ether, yielding a light yellow powder (0.9 g, 1.78 mmol). Yield= 83%, TLC (silica gel, DCM/MeOH: 9/1): R_f =0.23. ESI MS analysis gave the molecular weight at 406.2 (in agreement with the calculated molecular weight of 405.41).

[0294] Example 14

[0295] Camptothecin-20-(S)-[O-(N-succinyl-glycyl)]

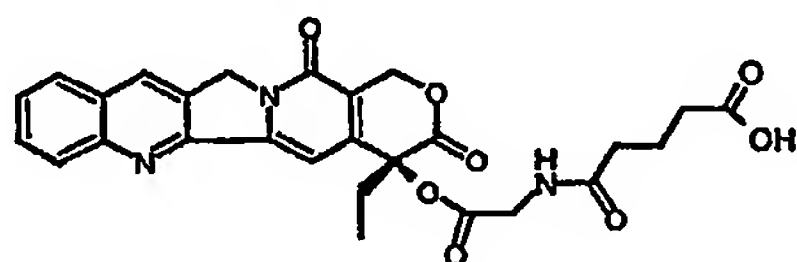


[0296]

[0297] A mixture of camptothecin-20-(S)-(O-glycyl) TFA (0.9 g, 1.7 mmol), succinic anhydride (0.35g, 3.5 mmol, 2 eq.), and triethylamine (0.72 mL, 3eq.) in DMF (10 mL) was stirred at room temperature for 5 min. The precipitate formed was collected by filtration. The solid collected was suspended in cold water (10 mL). The pH of the water suspension was adjusted to 2 by adding 5% aqueous citric acid solution. After stirring at 0 °C for 0.5 h, the precipitate was filtered, washed with cold water and ether, and dried under reduced pressure. 0.88 g (1.58 mmol) of a solid was obtained. The yield was 99 %. ESI MS analysis gave the molecular weight at 505.7 (in agreement with the calculated molecular weight of 505.49). Purity was 99% based on analytical HPLC analysis.

[0298] Example 15

[0299] Camptothecin-20-(S)-[O-(N-glutaryl-glycyl)]

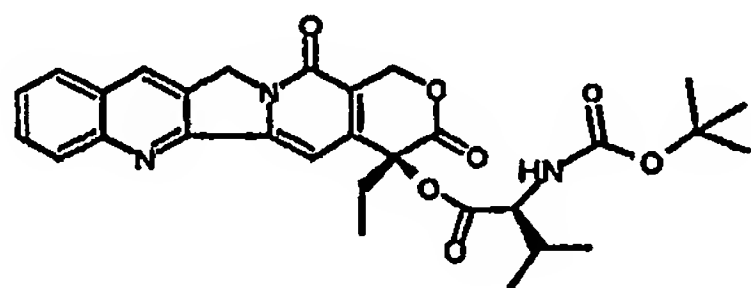


[0300]

[0301] The titled compound was synthesized substantially according to the procedure described in Example 14 by using glutaric anhydride. The yield was 75%. ESI MS analysis gave the molecular weight at 520.5 (in agreement with the calculated molecular weight of 519.52). Purity was 98% based on analytical HPLC analysis.

[0302] Example 16

[0303] Camptothecin-20-(S)-[O-(Boc-Valyl)]



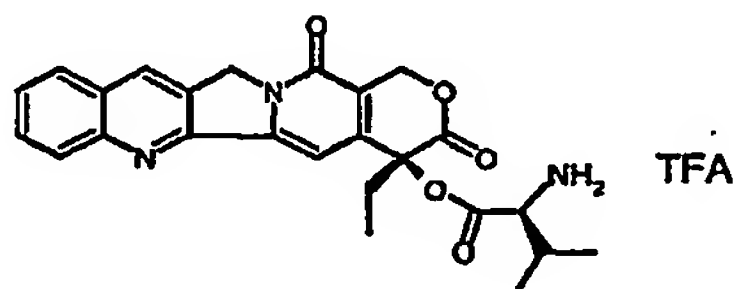
[0304]

[0305] To a suspension of camptothecin (350 mg) and DMAP (180 mg) in DCM (10 mL) at 0 °C was added a DCM solution of Boc-Val-F (2 eq.), which was prepared by using a literature method (Carpino et al., J.Org.Chem., 56, 2611, 1991). After stirring at 0-5 °C for 30 minutes, the mixture was warmed to room temperature and the stirring continued overnight. The mixture was diluted with chloroform (30 mL), washed with water, 10% citric acid aqueous solution and saturated NaHCO₃, dried over MgSO₄, and filtered. After removing the solvents under reduced

pressure, the residue was purified by a chromatography on a silica gel column eluting with chloroform/acetone (9:1). The fractions containing the desired product were pooled and concentrated under reduced pressure, resulting in a solid.

[0306] Example 17

[0307] Camptothecin-20-(S)-(O-Valyl) TFA salt

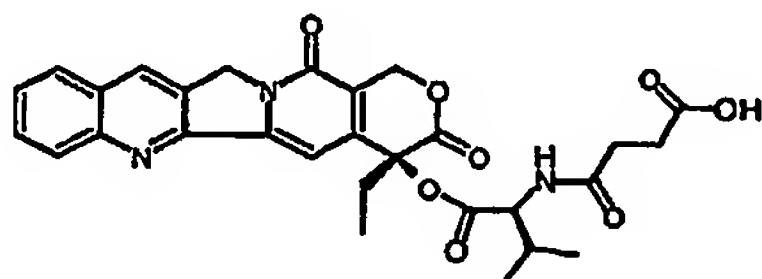


[0308]

[0309] Camptothecin-20-(S)-[O-(Boc-Valinyl)] obtained in Example 16 was treated with 35% TFA in chloroform (10 mL) for 30 min. TFA and solvent were removed *in vacuo*, yielding a solid. ESI MS analysis gave the molecular weight at 448.4 (in agreement with the calculated molecular weight of 447.50).

[0310] Example 18

[0311] Camptothecin-20-(S)-[O-(N-succinyl-Valyl)]

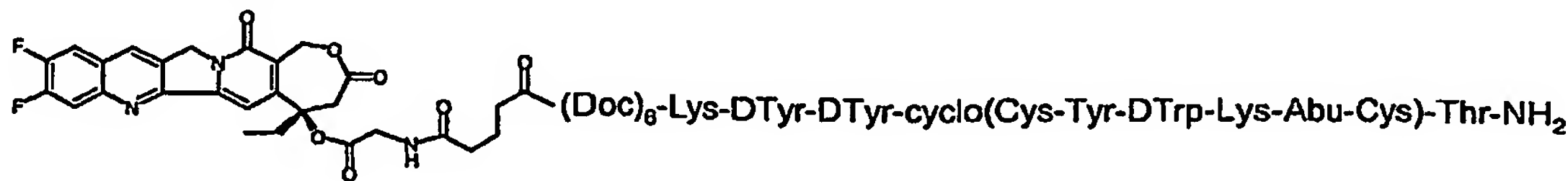


[0312]

[0313] To a mixture of camptothecin-20-(S)-(O-Valyl) TFA salt (150 mg), succinic anhydride (4 eq.), and DMAP (2 eq.) in chloroform (10 mL) was added triethylamine (6 eq.). After stirring at room temperature overnight, the mixture was diluted with chloroform (20 mL). The resulting solution was washed with water and aqueous citric acid solution, dried over MgSO₄, and filtered. Solvent was removed *in vacuo* and the residue was triturated with acetone. 120 mg of the title compound was obtained. TLC (silica gel, chloroform/methanol=9:1): R_f=0.22. ESI MS analysis gave the molecular weight at 548.2 (in agreement with the calculated molecular weight of 547.57).

[0314] Example 19

[0315] {5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione-5-O-glycyl-glutaryl}-Doc-Doc-Doc-Doc-Doc-Doc-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

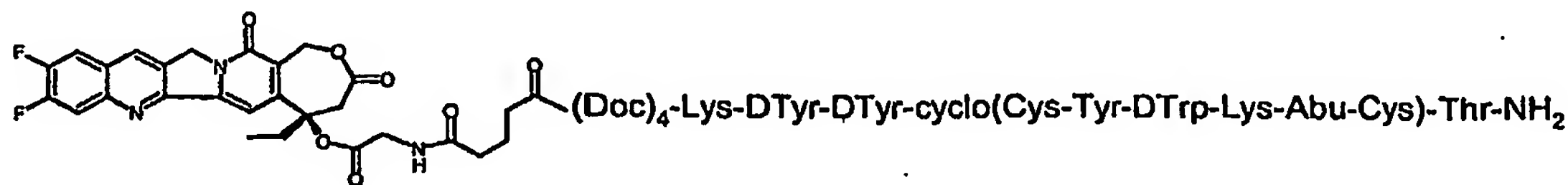


[0316]

[0317] H-Doc-Doc-Doc-Doc-Doc-Doc-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin (0.196 mmol) of Example 3 was mixed with 5-O-(N-glutaryl-glycyl)-5-(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione (0.123 g, 0.22 mmol, 1.1 eq.) (Example 10), DIC (136 μ L, 0.88 mmol, 4.4 eq.) and 1-hydroxy-7-azabenzotriazol (HOAT) (30 mg, 0.22 mmol, 1.1 eq.) in 5 mL of DCM. The mixture was shaken for 2 days. The resin was washed successively with DMF, methanol and DCM. After drying in the air, the resin was treated with a mixture of TFA, H₂O and triisopropylsilane (TIS) (9.5 mL / 0.85 mL / 0.8 mL) for 2h. The resin was filtered off and the filtrate was poured into 100 mL of cold ether. The precipitate was collected after centrifuge. The crude product was dissolved in 100 mL of 5% AcOH aqueous solution, to which iodine methanol solution was added dropwise until yellow color maintained. The reaction solution was stirred for additional 1h. 10% Na₂S₂O₃ water solution was added to quench the excess iodine. The crude product in the solution was purified on preparative HPLC system with a column (4 x 43 cm) of C₁₈ DYNAMAX-100 A⁰ (Varian, Walnut Creek, CA). The column was eluted with a linear gradient from 80% A and 20% B to 55%A and 45% B in 50 min., where A was 0.1% TFA in water and B was 0.1% TFA in acetonitrile. The fractions were checked by an analytical HPLC. Those containing pure product were pooled and lyophilized to dryness. Yield: 25%. The purity was 99.9% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2761.1 (in agreement with the calculated molecular weight of 2761.04).

[0318] Example 20

[0319] {5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione-5-O-glycyl-glutaryl)-Doc-Doc-Doc-Doc-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

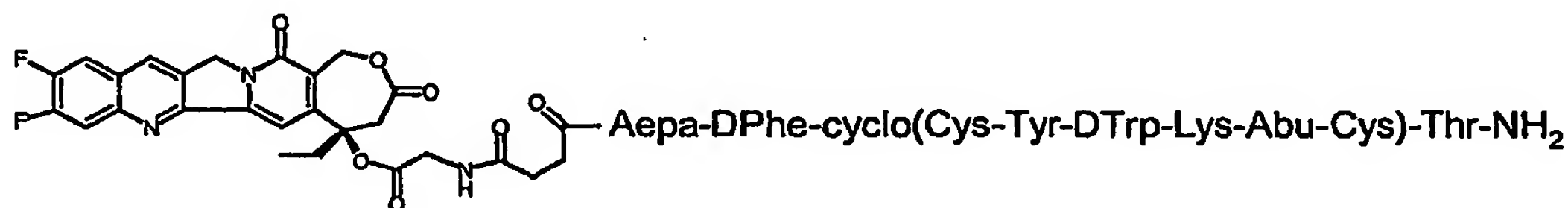


[0320]

[0321] The titled compound was synthesized substantially according to the procedure described in Example 19 by using H-Doc-Doc-Doc-Doc-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin of Example 2. Yield was 21.4 %. Purity: 99% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2471.2 (in agreement with the calculated molecular weight of 2471.727).

[0322] Example 21

[0323] {5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione-5-O-glycyl-succinyl}-Aepa-DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

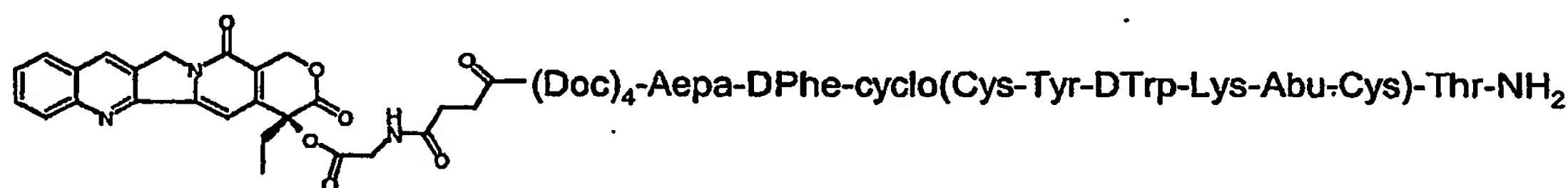


[0324]

[0325] The titled compound was synthesized substantially according to the procedure for Example 19 by using 5-O-(N-succinyl-glycyl)-5-(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3*H*,15*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione (Example 11) and H-Aepa-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin (Example 7). Yield was 48 %, Purity: 99.9% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 1739.8 (in agreement with the calculated molecular weight of 1740.14).

[0326] Example 22

[0327] Camptothecin-20-(S)-O-glycyl-succinyl-Doc-Doc-Doc-Doc-Aepa-DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

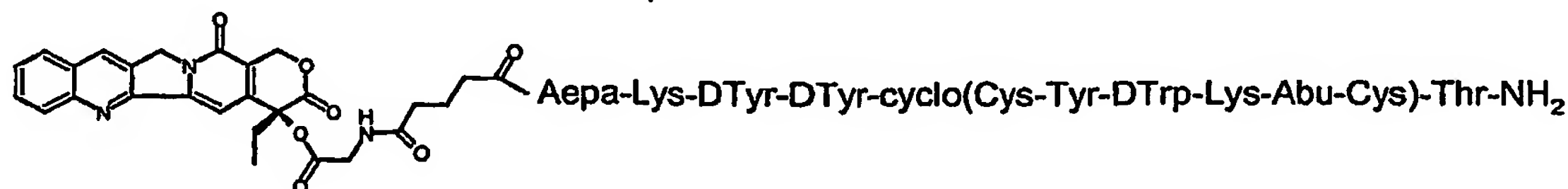


[0328]

[0329] The titled compound was synthesized substantially according to the procedure for Example 19 by using camptothecin-20-(S)-[O-(N-succinyl-glycyl)] (Example 14) and H-Doc-Doc-Doc-Doc-Aepa-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)- Rink Amide MBHA Resin. Yield was 32 %. Purity was 99 % based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2269.0. (in agreement with the calculated molecular weight of 2269.8).

[0330] Example 23

[0331] Camptothecin-20-(S)-O-glycyl-glutaryl-Aepa-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

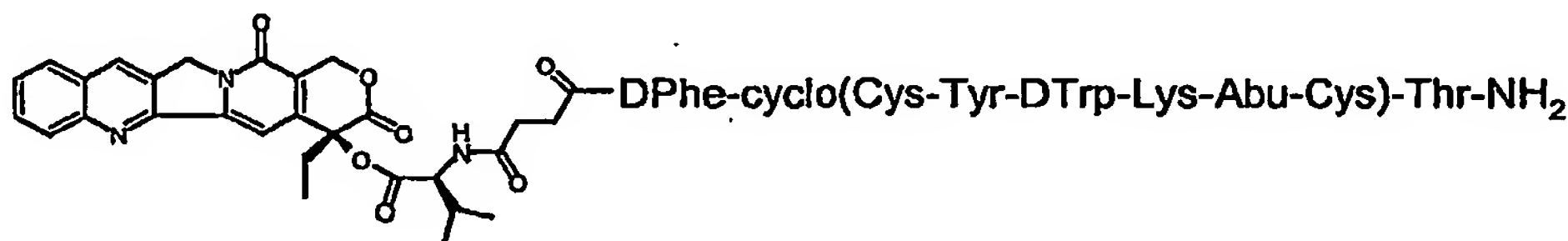


[0332]

[0333] The titled compound was synthesized substantially according to the procedure in Example 19 by using camptothecin-20-(S)-[O-(glutaryl-glycyl)] (Example 15) and H-Aepa-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin (Example 4). Yield was 11%. Purity was 95% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2008.9 (in agreement with the calculated molecular weight of 2009.2).

[0334] Example 24

[0335] Camptothecin-20-(S)-O-Valyl-succinyl-DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

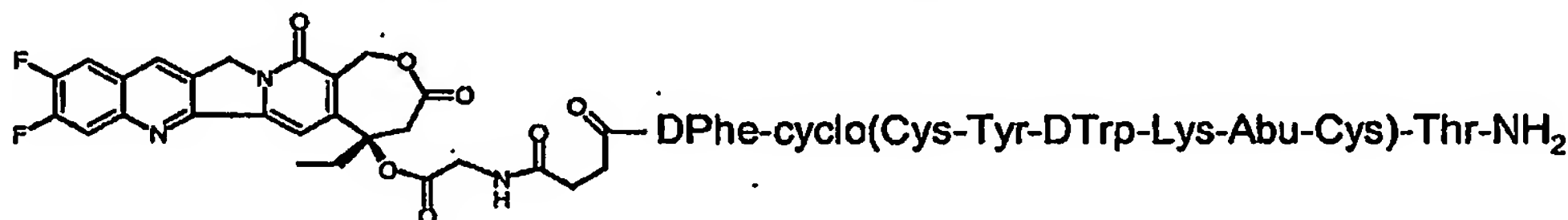


[0336]

[0337] The titled compound was synthesized substantially according to the procedure in Example 19 by using camptothecin-20-(S)-[O-(N-succinyl-Valyl)] (Example 18) and H-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin (Example 6). 145 mg of a pale yellow solid was obtained. ESI MS analysis gave the molecular weight at 1562.4 (in agreement with the calculated molecular weight of 1561.8).

[0338] Example 25

[0339] {5-(R)-Ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione-5-O-glycyl-succinyl}-DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂



[0340]

[0341] The titled compound was synthesized substantially according to the procedure for Example 19 by using 5-(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione-5-O-(N-succinyl-glycyl) (Example 11) and H-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin (Example 6). A yellow solid was obtained. ESI MS analysis gave the molecular weight at 1570.2 (in agreement with the calculated molecular weight of 1569.72).

[0342] Example 26

[0343] H-Aepa-(Doc)₄-Gln(Trt)-Trp(Boc)-Ala-Val-βAla-His(Trt)-Leu-Leu-Rink Amide MBHA resin

[0344] The titled protected peptide-resin was synthesized substantially according to the procedure described for Example 5. Fmoc-His(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, and Fmoc-βAla-OH were purchased from AnaSpec (San Jose, CA).

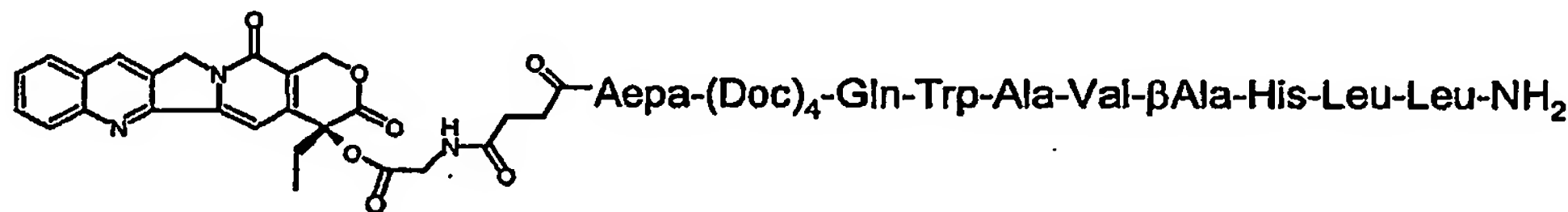
[0345] Example 27

[0346] H-Aepa-(Doc)₄-DPhe-Gln(Trt)-Trp(Boc)-Ala-Val-βAla-His(Trt)-Leu-Leu-Rink Amide MBHA resin

[0347] The titled protected peptide-resin was synthesized substantially according to the procedure described for Example 26.

[0348] Example 28

[0349] Camptothecin-20-(S)-O-glyciny succinyl-Aepa-(Doc)₄-Gln-Trp-Ala-Val-βAla-His-Leu-Leu-NH₂

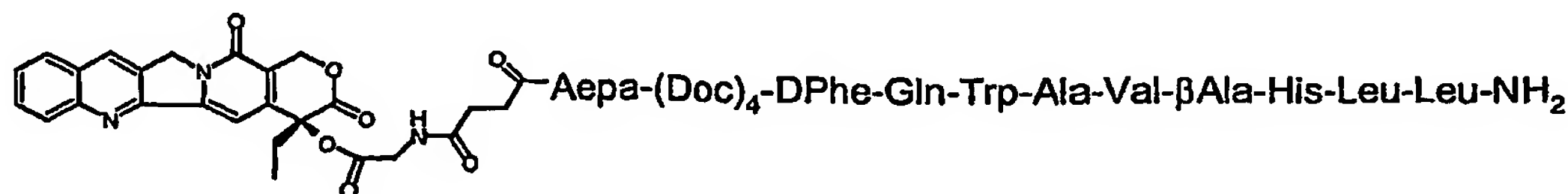


[0350]

[0351] A mixture of H-Aepa-(Doc)₄-Gln(Trt)-Trp(Boc)-Ala-Val-βAla-His(Trt)-Leu-Leu-Rink Amide MBHA resin (0.125 mmol) of Example 26, camptothecin-20-(S)-[O-(N-glycyl-succinyl)] (Example 14) (0.138 mmol, 1.1 eq.), DIC (0.55 mmol, 4.4 eq.), and HOBt (0.275 mmol, 2.2 eq.) in DCM (7 mL) and DMF (7mL) was shaken at room temperature for 5 days. The peptide was cleaved off from the resin using a solution of TFA, H₂O and TIS (9.5 mL / 0.85 mL / 0.8 mL) for 2 hours. The resin was filtered off and the peptide was precipitated using diethyl ether. After centrifuging the suspension, a pellet of crude peptide was obtained. The crude product was purified on a preparative HPLC system with a Microsorb C₁₈ column, eluting with a linear gradient from 100% A and 0% B to 20%A and 80% B in 80 min. A was 0.1% TFA in water and B was 0.1% TFA in acetonitrile. The fractions were checked by an analytical HPLC. The fractions containing the desired product were pooled and lyophilized to dryness. Purity was 96.1 % based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2172.9 (in agreement with the calculated molecular weight of 2173.44).

[0352] Example 29

[0353] Camptothecin-20-(S)-O-glyciny succinyl-Aepa-(Doc)₄-DPhe-Gln-Trp-Ala-Val-βAla-His-Leu-Leu-NH₂

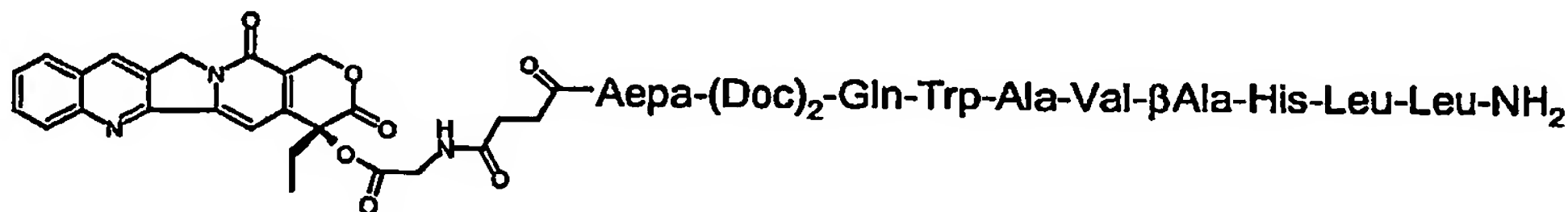


[0354]

[0355] The titled peptide was synthesized substantially according to the procedure described for Example 28. Purity was 99.9 % based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2321.1 (in agreement with the calculated molecular weight of 2320.62).

[0356] Example 30

[0357] Camptothecin-20-(S)-O-glyciny succinyl-Aepa-(Doc)₂-Gln-Trp-Ala-Val-βAla-His-Leu-Leu-NH₂

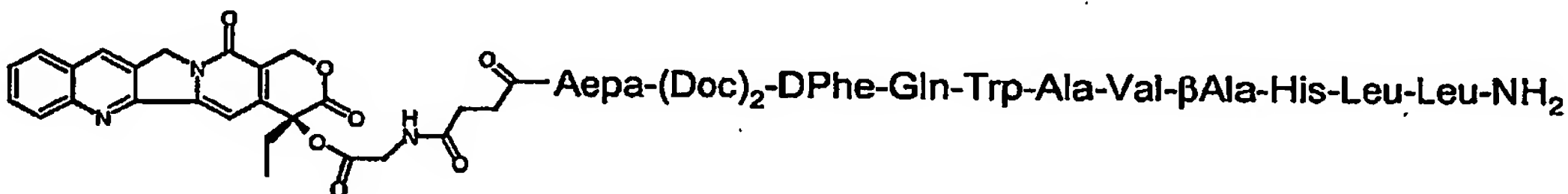


[0358]

[0359] The titled peptide was synthesized substantially according to the procedure described for Example 28. Purity was 99.9 % based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 1882.8 (in agreement with the calculated molecular weight of 1883.13).

[0360] Example 31

[0361] Camptothecin-20-(S)-O-glyciny succinyl-Aepa-(Doc)₂-DPhe-Gln-Trp-Ala-Val-βAla-His-Leu-Leu-NH₂

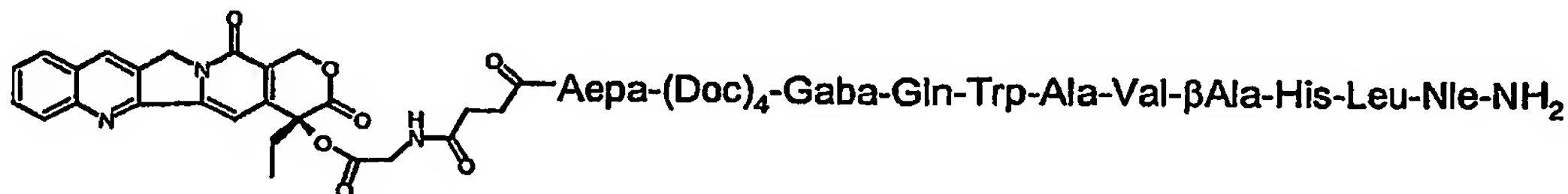


[0362]

[0363] The titled peptide was synthesized substantially according to the procedure described for Example 28. Purity was 99.9 % based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2030.7 (in agreement with the calculated molecular weight of 2030.30).

[0364] Example 32

[0365] Camptothecin-20-(S)-O-glyciny succinyl-Aepa-(Doc)₄-Gaba-Gln-Trp-Ala-Val-βAla-His-Leu-Nle-NH₂



[0366]

[0367] The titled peptide is synthesized substantially according to the procedure described for Example 28 by using Aepa-(Doc)₄-Gaba-Gln(Trt)-Trp(Boc)-Ala-Val-βAla-His(Trt)-Leu-Nle-Rink Amide MBHA resin.

[0368] Example 33

[0369] pGlu-His(Trt)-Trp(Boc)-Ser(tBu)-Tyr(tBu)-DLys[N^ε-Aepa]-Leu-Arg(Pbf)-Pro-Gly-Rink Amide MBHA resin

[0370] The titled peptide resin was synthesized substantially according to the procedure described in Example 1. Fmoc-Arg(Pbf)-OH, Fmoc-Ser(tBu)-OH, Fmoc-His(Trt)-OH, Fmoc-Pro-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-DLys(Dde)-OH were purchased from Novabiochem, San Diego, CA. pGlu-OH was from Chem-Impex Internatoinal, Wood Dale, IL. The synthesis was carried out on a 0.25 mmol scale. The Fmoc groups are removed by treatment with 20% piperidine in N-methylpyrrolidone (NMP) for 30 min. After finishing the assembly of pGlu-His(Trt)-Trp(Boc)-Ser(tBu)-Tyr(tBu)-DLys(Dde)-Leu-Arg(Pbf)-Pro-Gly-Rink Amide MBHA resin, the protected peptide-resin was transferred into a reaction vessel on a shaker for manual synthesis. The Dde protecting group on DLys residue was removed by using 2% hydrazine in DMF for 0.5 h. The resin was washed completely with DMF, MeOH and DCM and shaken for 2h with the pre-activated Fmoc-Aepa-OH ester solution (described In Example 4) in DMF containing 0.5 mL of DIEA. The resin was washed with DMF and treated with 20% piperidine in DMF to remove Fmoc protecting group on Aepa residue. The protected peptide-resin was washed completely by using DMF and DCM.

[0371] Dde=[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]

[0372] Example 34

[0373] pGlu-His(Trt)-Trp(Boc)-Ser(tBu)-Tyr(tBu)-DLys[N^ε-(Aepa-(Doc)₄-)]-Leu-Arg(Pbf)-Pro-Gly-Rink Amide MBHA resin

[0374] The titled protected peptide resin was synthesized substantially according to the procedure in Example 2 by using pGlu-His(Trt)-Trp(Boc)-Ser(tBu)-Tyr(tBu)-DLys[N^ε-Aepa]-Leu-Arg(Pbf)-Pro-Gly-Rink Amide MBHA resin (Example 33).

[0375] Example 35

[0376] H-(Doc)₄-Aepa-Caeg-DCys(Trt)-3Pal-DTrp(Boc)-Lys(Boc)-DCys(Trt)-Thr(Bzl)-Tyr(tBu)-Rink Amide MBHA resin

[0377] The titled protected peptide resin is synthesized substantially according to the procedure for Example 5. Fmoc-Thr(Bzl)-OH, Fmoc-DCys(Trt)-OH, and Fmoc-3Pal-OH are from Chem-Impex Internatoinal, Wood Dale, IL. Fmoc-DTrp(Boc)-OH, Fmoc-Lys(Boc)-OH and Fmoc-Tyr(tBu)-OH are from AnaSpec, San Jose, CA. Fmoc-Caeg(Bhoc)-OH is from PepSeptive Biosystems, Framingham, Mass.

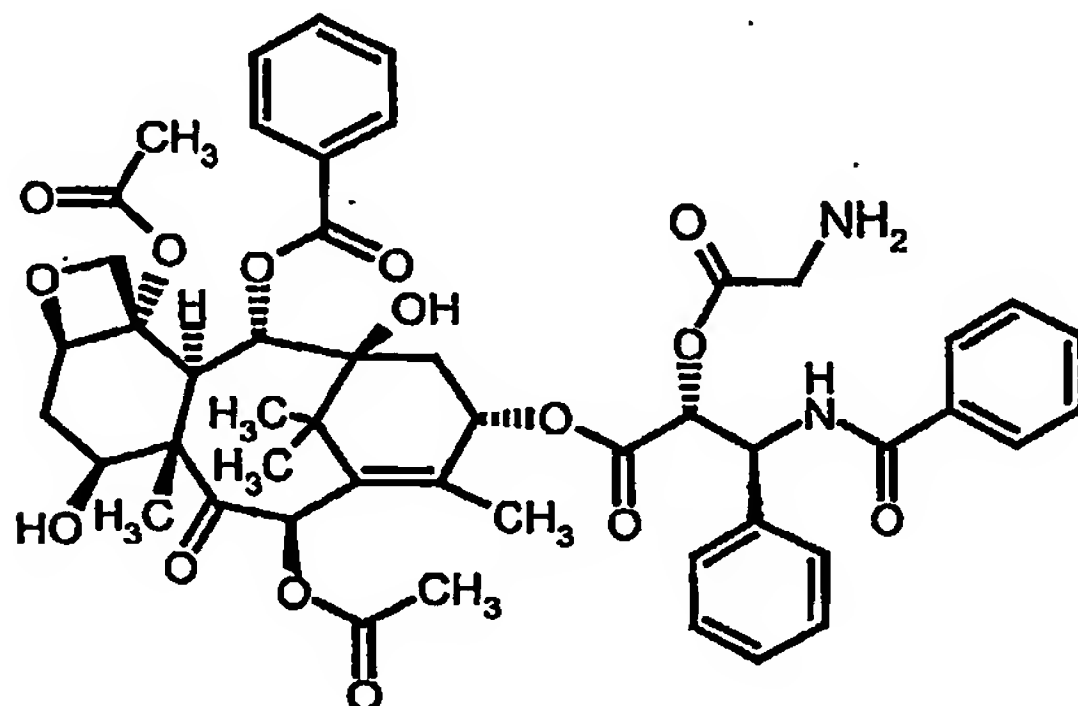
[0378] Example 36

[0379] H-(Doc)₄-Aepa-DPhe-Cys(Trt)-3ITyr-DTrp(Boc)-Lys(Boc)-Val-Cys(Trt)-Thr(tBu)-Rink Amide MBHA resin

[0380] The titled protected peptide resin is synthesized substantially according to the procedure for Example 5. Fmoc-3ITyr-OH and Fmoc-DPhe-OH are from Chem-Impex Internatoinal, Wood Dale, IL.

[0381] Example 37

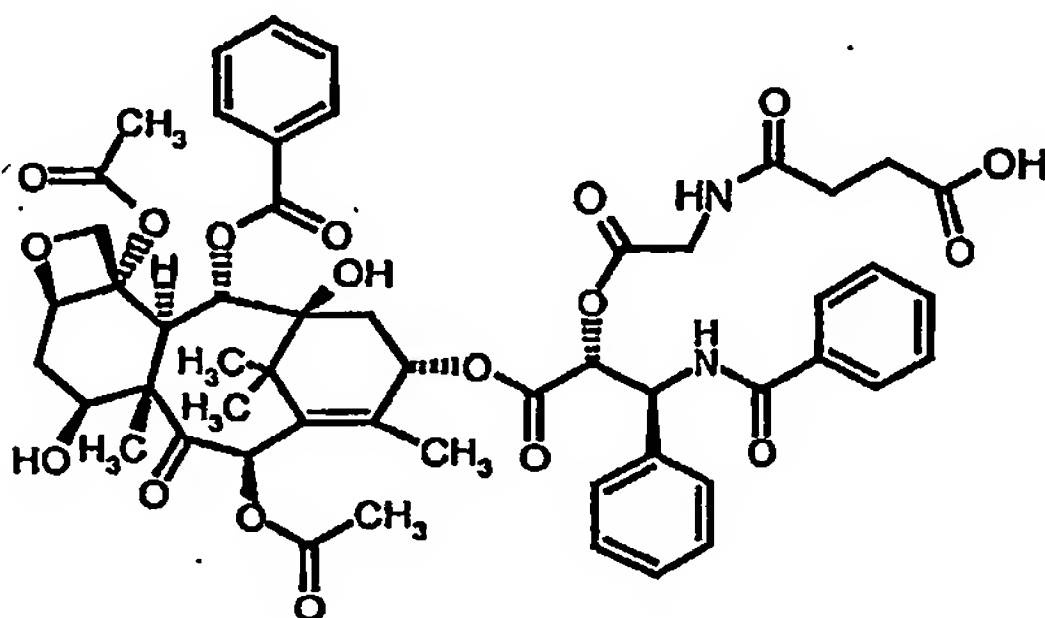
[0382] Paclitaxel-2'-O-glycyl



[0383]

[0384] To a solution of Boc-Gly-OH (53 mg) and paclitaxel (215 mg) in 10 mL of dichloromethane was added 4-dimethylaminopyridine (DMAP, 10 mg) followed by EDC (58 mg). After stirring at room temperature overnight, the reaction mixture was diluted with 20 mL of dichloromethane and the mixture was washed with 10% aqueous citirc acid, saturated NaHCO₃ and water, dried over MgSO₄, and filtered. The solvent was removed *in vacuo*. The crude product was treated with 30% TFA in dichloromethane for 45 min at room temperature. TFA and the solvent were removed *in vacuo*, yielding a solid. 0.256 g, ESI MS analysis gave the molecular weight at 911.0 (in agreement with the calculated molecular weight of 911.1).

[0385] Example 38



[0386]

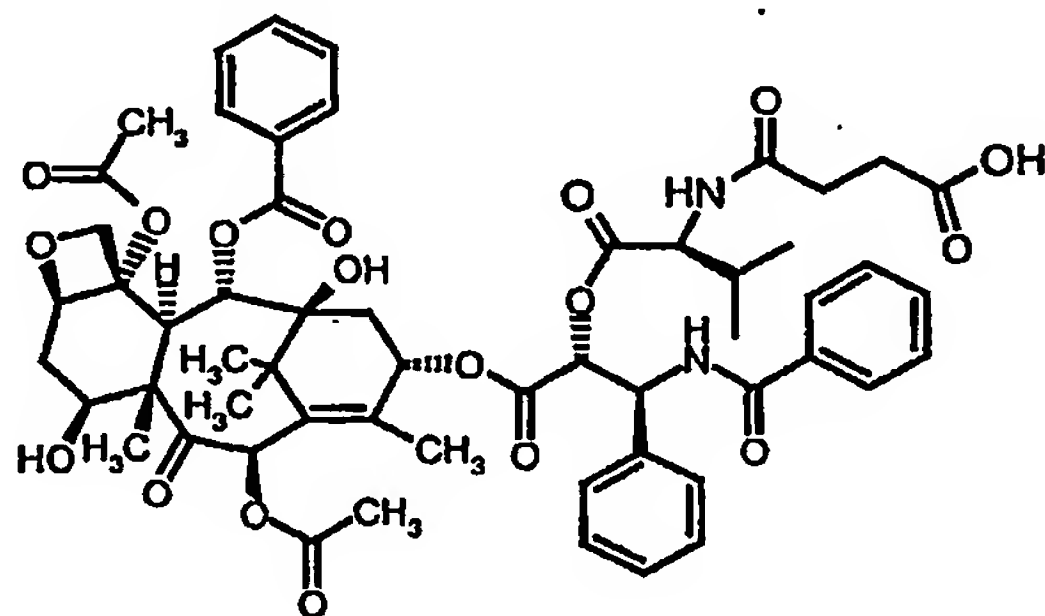
[0387] Paclitaxel-2'-O-(N-glycyl-succinyl)

[0388] A mixture of paclitaxel-2'-O-glycyl TFA salt (127 mg, 1 eq.) and succinic anhydride (150 mg, 12 eq) in 5 mL of pyridine was stirred overnight at room temperature. The solvent was removed *in vacuo*. The residue was triturated with water for 1 hour and the precipitate was

collected by filtration, washed with water and dried, yielding a solid (94.8 mg). ESI MS analysis gave the molecular weight at 1010.9 (in agreement with the calculated molecular weight of 1011.06).

[0389] Example 39

[0390] Paclitaxel-2'-O-(N-valyl-succinyl)

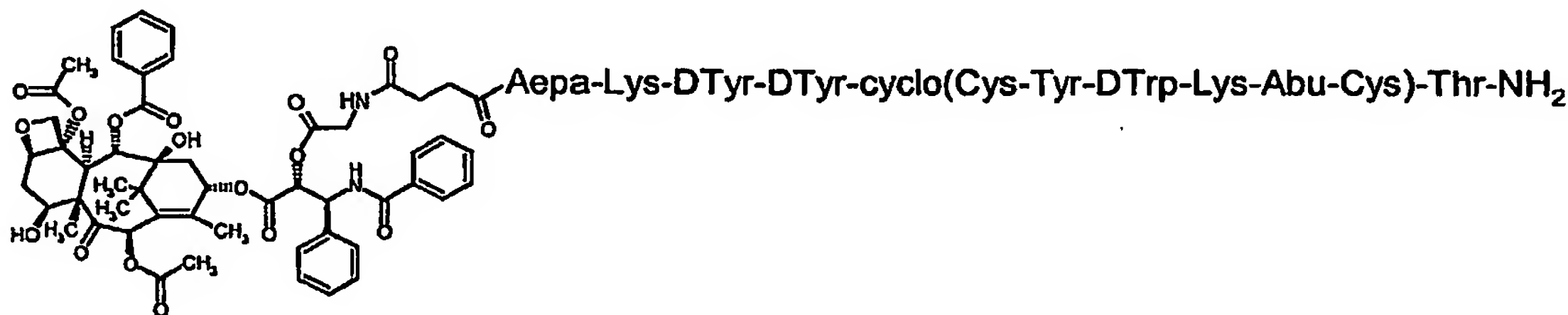


[0391]

[0392] The titled compound was synthesized substantially according to the procedures described in Examples 37 and 38 by using Boc-Val-OH. ESI MS analysis gave the molecular weight at 1052.5 (in agreement with the calculated molecular weight of 1053.27).

[0393] Example 40

[0394] Paclitaxel-2'-O-Gly-Succinyl-Aepa-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂



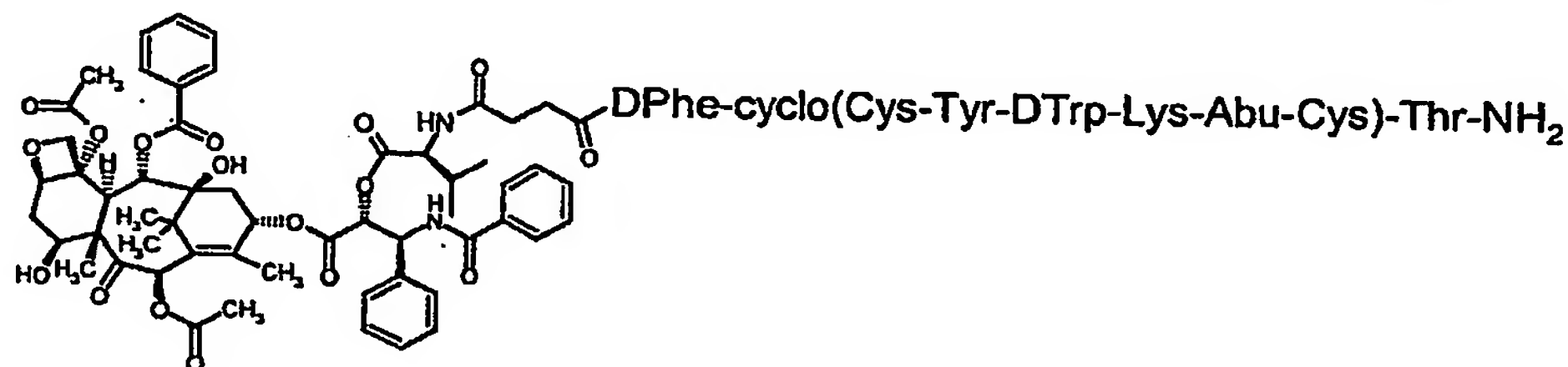
[0395]

[0396] A mixture of H-Aepa-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Rink Amide MBHA resin (0.1 mmol) (Example 4), paclitaxel-2'-O-(N-glycyl-succinyl) (Example 39) (1.1 eq.), DIC (136 μ L, 4.4 eq.), and HOAT (30 mg, 1.1 eq.) in 5 mL of DCM was shaken for 2 days. The resin was washed successively with DMF, methanol and DCM. After drying in the air, the resin was treated with a mixture of TFA, H₂O and triisopropylsilane (TIS) (9.5 mL / 0.85 mL / 0.8 mL) for 2 h. The resin was filtered off and the filtrate was poured into 100 mL of cold ether. The precipitate was collected after centrifuge. The crude product was dissolved in a mixed solution system (100 mL of 5% acetic acid aqueous solution and 30 mL of acetonitrile). To the solution was added dropwise iodine methanol solution until the yellow color maintained. The reaction solution was stirred for additional 45 min.

10% Na₂S₂O₃ water solution was added to quench excess iodine. The crude product in the solution was purified on a preparative HPLC system with a column (4x43cm) of C₁₈ DYNAMAX-100 A⁰ (Varian, Walnut Creek, CA). The column was eluted with a linear gradient from 80% A and 20% B to 55%A and 45% B in 50 min., where A was 0.1% TFA in water and B was 0.1% TFA in acetonitrile. The fractions were checked by an analytical HPLC. Those containing pure product were pooled and lyophilized to dryness. The purity was 98% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2500.9 (in agreement with the calculated molecular weight of 2501.0).

[0397] Example 41

[0398] Paclitaxel-2'-O-Val-Succinyl-DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

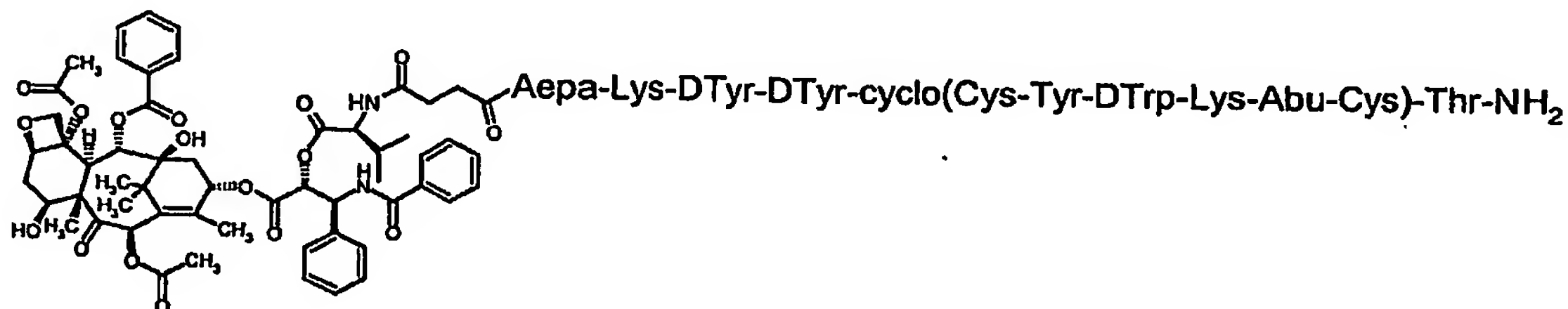


[0399]

[0400] The titled peptide was synthesized substantially according to the procedure described in Example 40. The purity was 99% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2066.2 (in agreement with the calculated molecular weight of 2067.4).

[0401] Example 42

[0402] Paclitaxel-2'-O-Val-Succinyl-Aepa-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

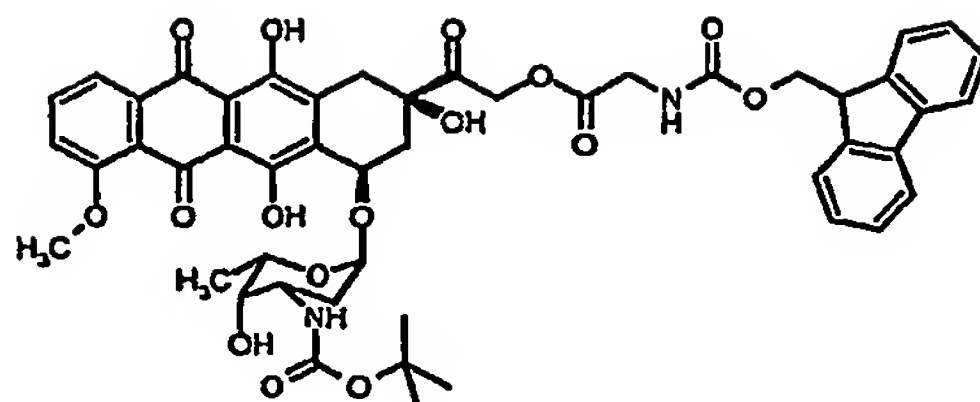


[0403]

[0404] The titled peptide was synthesized substantially according to the procedure described in Example 40. The purity was 95% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2544.3 (in agreement with the calculated molecular weight of 2543.9).

[0405] Example 43

[0406] N-Boc-Doxorubicin-14-O-(Fmoc-glycine) ester

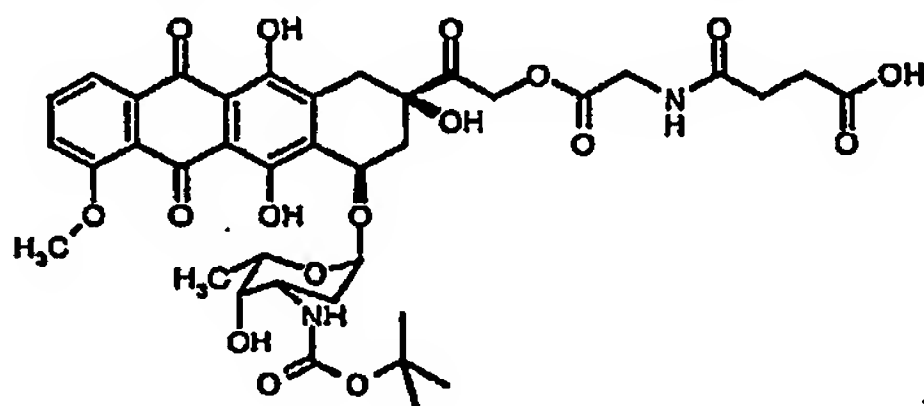


[0407]

[0408] To a solution of doxorubicin-HCl (190 mg) in DMF (5 mL) is added (BOC)₂O (1.2 eq), followed by diisopropylethylamine (2.5 eq.). After stirring for 3 hours, volatile substances are removed *in vacuo* and the residue is treated with water. The solid is collected by filtration, washed with water and dried. The resulting product is dissolved in DMF (10 mL). To it are added Fmoc-Gly-OH (1.2 eq.), DMAP (0.2 eq.) and EDC (1.2 eq). The mixture is stirred at room temperature for 4h. After evaporation of the solvent, the residue is partitioned between chloroform-methanol and water. Organic layer is dried over MgSO₄ and filtered. Solvents are removed *in vacuo* and the residue is chromatographed on silica gel eluting with chloroform-methanol (9:1). The fractions containing the desired product are pooled and solvents are evaporated *in vacuo*.

[0409] Example 44

[0410] N-BOC-Doxorubicin-14-O-[(N-succinyl)glycine] ester

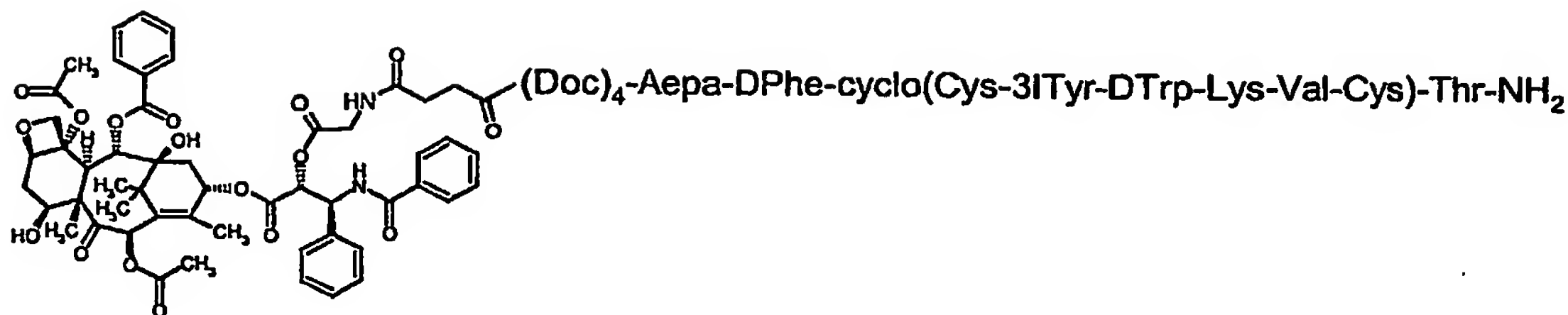


[0411]

[0412] To a solution of Boc-doxorubicin-14-O-(Fmoc-glycine) ester (100 mg) in DMF (5 mL) is added 1 mL of piperidine. After stirring for 2 hours at room temperature, the mixture is diluted with chloroform (20 mL). The mixture is washed with brine, dried over MgSO₄, and filtered. The solvents are removed *in vacuo* to a small volume (~5 mL). To the mixture are added succinic anhydride (4 eq.), DMAP (2 eq.) and triethylamine (4 eq.). The solution is stirred at room temperature overnight. Volatile substances are removed *in vacuo*. The residue is triturated with 5% aqueous citric acid. Precipitate is collected by filtration, washed with water, and dried.

[0413] Example 45

[0414] pGlu-His-Trp-Ser-Tyr-DLys[N^ε-(doxorubicin-14-O-glycyl-succinyl-Aepa-(Doc)₄-)]-Leu-Arg-Pro-Gly-NH₂

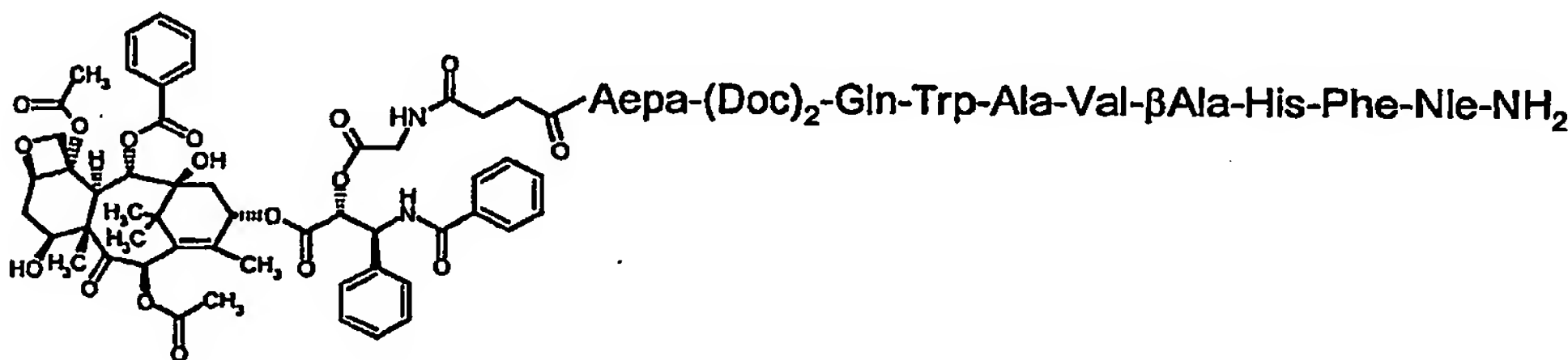


[0427]

[0428] The titled compound is synthesized substantially according to the procedure for Example 40 by using H-(Doc)₄-Aepa-DPhe-Cys(Trt)-3ITyr-DTrp(Boc)-Lys(Boc)-Val-Cys(Trt)-Thr(tBu)-Rink Amide MBHA resin (Example 36) and paclitaxel-2'-O-(N-glycyl-succinyl) (Example 38).

[0429] Example 49

[0430] Paclitaxel-2'-O-glycyl-succinyl-Aepa-(Doc)₂-Gln-Trp-Ala-Val-βAla-His-Phe-Nle-NH₂

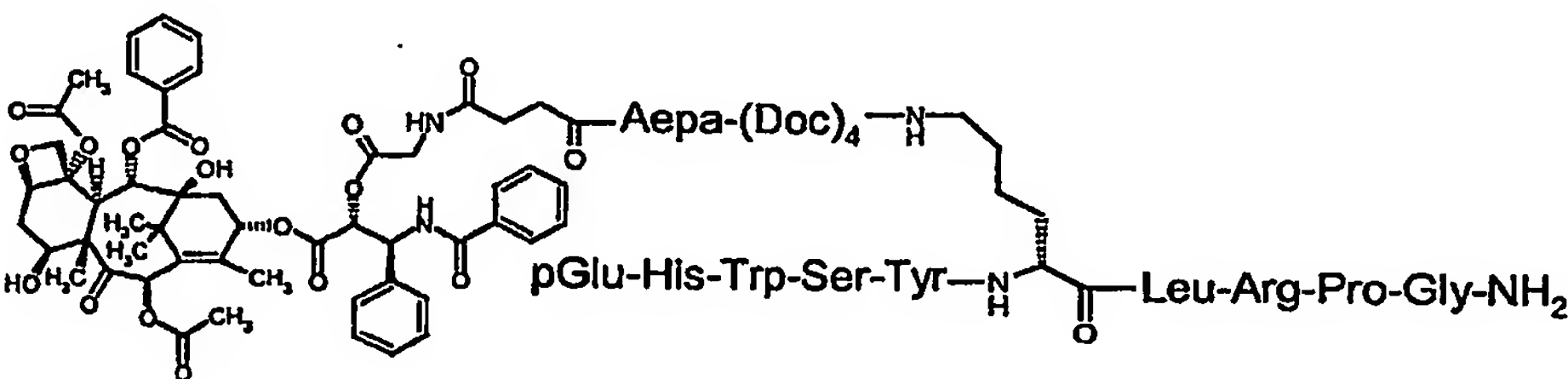


[0431]

[0432] The titled compound is synthesized substantially according to the procedure for Example 28 by using H-Aepa-(Doc)₂-Gln(Trt)-Trp(Boc)-Ala-Val-βAla-His(Trt)-Phe-Nle-Rink Amide MBHA resin and paclitaxel-2'-O-(N-glycyl-succinyl) (Example 38).

[0433] Example 50

[0434] pGlu-His-Trp-Ser-Tyr-DLys[N^ε-(paclitaxel-2'-O-glycyl-succinyl-Aepa-(Doc)₄)]-Leu-Arg-Pro-Gly-NH₂

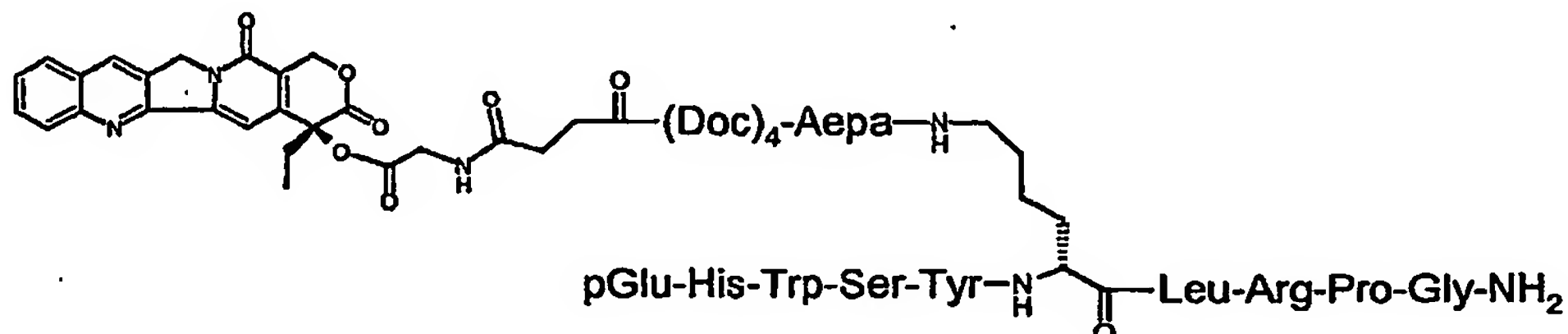


[0435]

[0436] The titled compound is synthesized substantially according to the procedure for Example 45 by using pGlu-His(Trt)-Trp(Boc)-Ser(tBu)-Tyr(tBu)-DLys[N^ε-(Aepa-(Doc)₄)]-Leu-Arg(Pbf)-Pro-Gly-Rink Amide MBHA resin (Example 34) and 2'-O-(N-succinyl-glycyl)-paclitaxel (Example 38).

[0437] Example 51

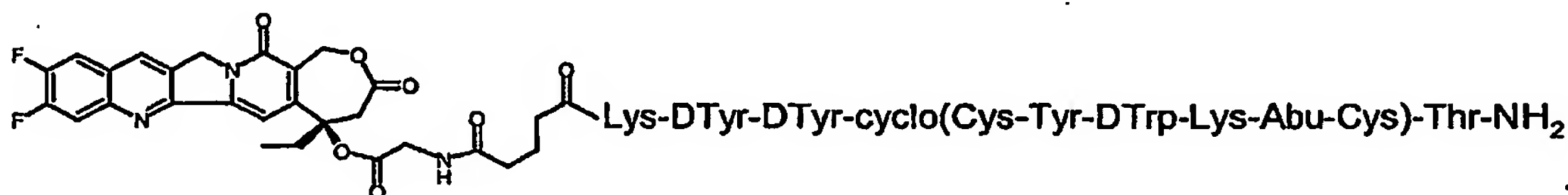
[0438] pGlu-His-Trp-Ser-Tyr-DLys[N^B-(camptothecin-20-(S)-O-glycinyI-succinyI-(Doc)₄-Aepa-)]-Leu-Arg-Pro-Gly-NH₂



[0439]

[0440] The titled compound is synthesized substantially according to the procedure for Example 50 by using camptothecin-20-(S)-[O-(N- succinyI-glycyl)] (Example 14).

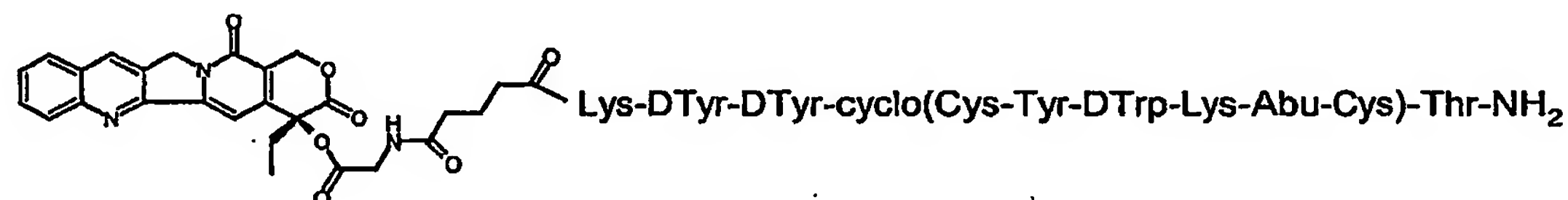
[0441] Example 52



[0442]

The title compound was synthesized substantially according to the procedure described in Example 19. Yield= 11 %. Purity was 99.9% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 1891.8 (in agreement with the calculated molecular weight of 1891.1).

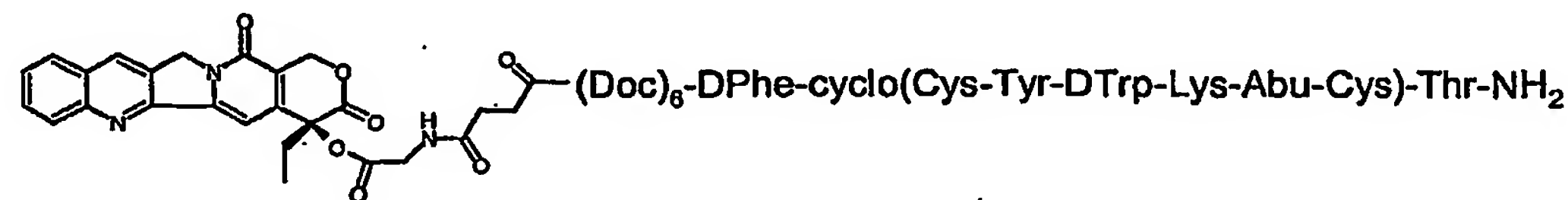
[0443] Example 53



[0444]

[0445] The title compound was synthesized substantially according to the procedure described in Example 19. Yield= 23 %. Purity was 99 % based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 1841.9 (in agreement with the calculated molecular weight of 1841.1).

[0446] Example 54

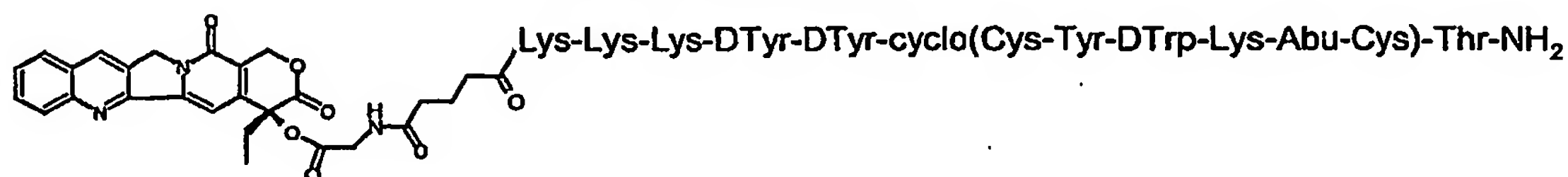


[0447]

[0448] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=18 %. Purity was 98 % based on analytical HPLC analysis. ESI MS

analysis gave the molecular weight at 2390.0 (in agreement with the calculated molecular weight of 2390.7).

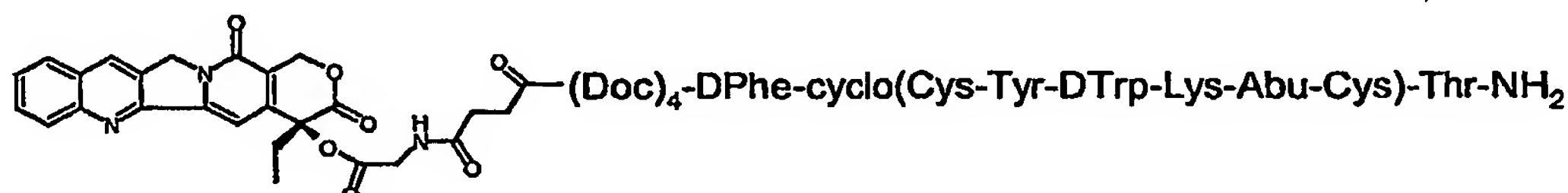
[0449] Example 55



[0450]

[0451] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=12 %. Purity was 100% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2097.0 (in agreement with the calculated molecular weight of 2097.4).

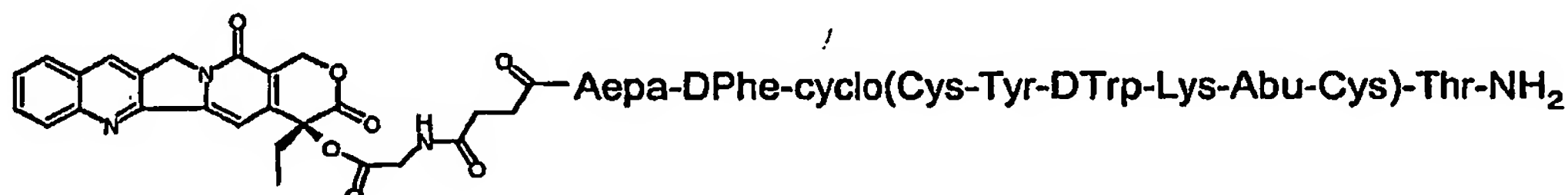
[0452] Example 56



[0453]

[0454] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=31%. Purity was 100% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2100.9 (in agreement with the calculated molecular weight of 2100.3).

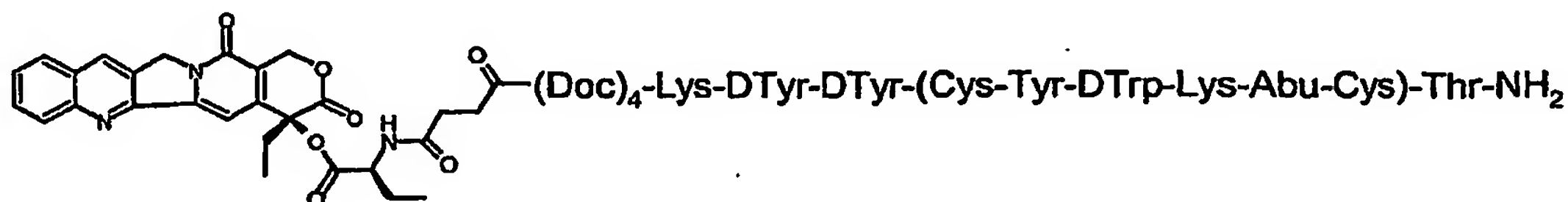
[0455] Example 57



[0456]

[0457] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=21%. Purity was 97% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 1688.0 (in agreement with the calculated molecular weight of 1688.9).

[0458] Example 58

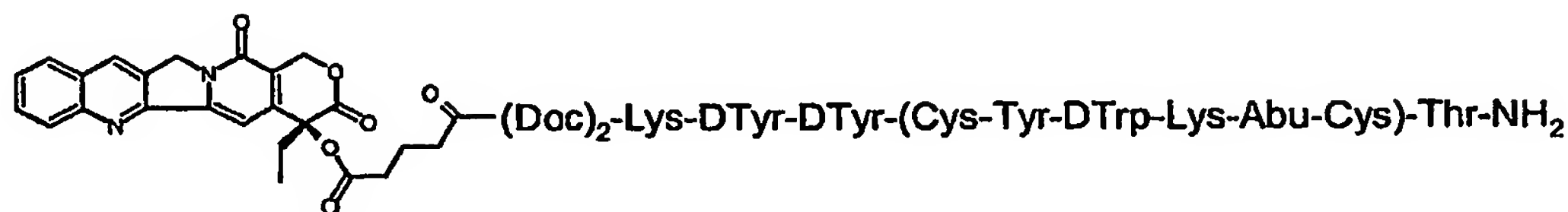


[0459]

[0460] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=23%. Purity was 95% based on analytical HPLC analysis. ESI MS

analysis gave the molecular weight at 2435.2 (in agreement with the calculated molecular weight of 2435.8).

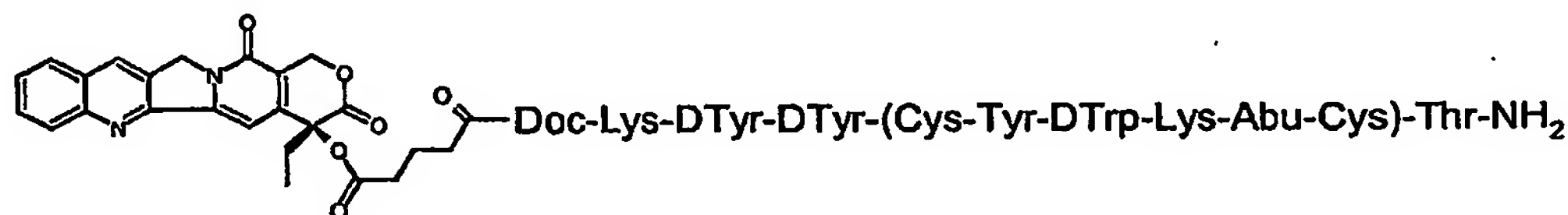
[0461] Example 59



[0462]

[0463] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=11%. Purity was 95% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2074.0 (in agreement with the calculated molecular weight of 2074.4).

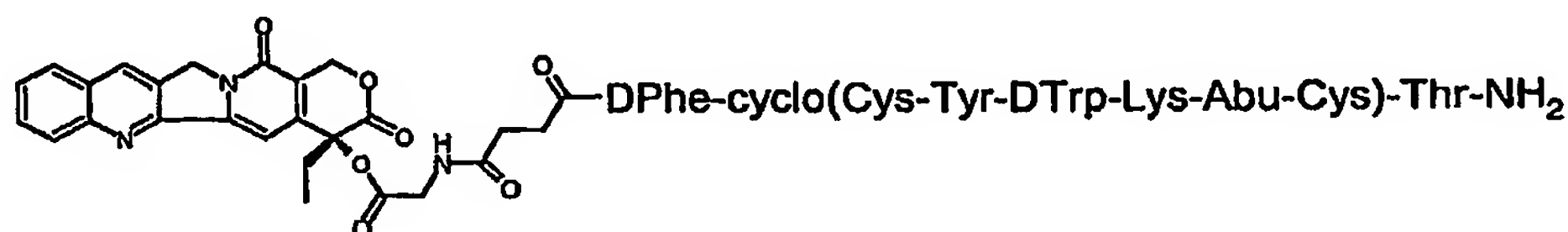
[0464] Example 60



[0465]

[0466] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=16%. Purity was 95% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 1929.5 (in agreement with the calculated molecular weight of 1929.2).

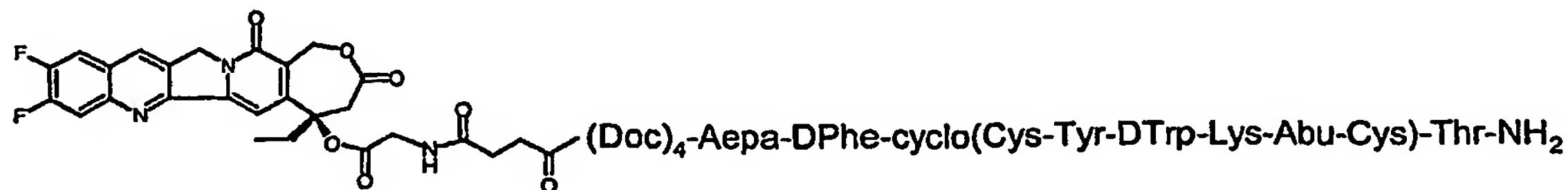
[0467] Example 61



[0468]

[0469] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=15.6%. Purity was 94% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 1520.1 (in agreement with the calculated molecular weight of 1519.71).

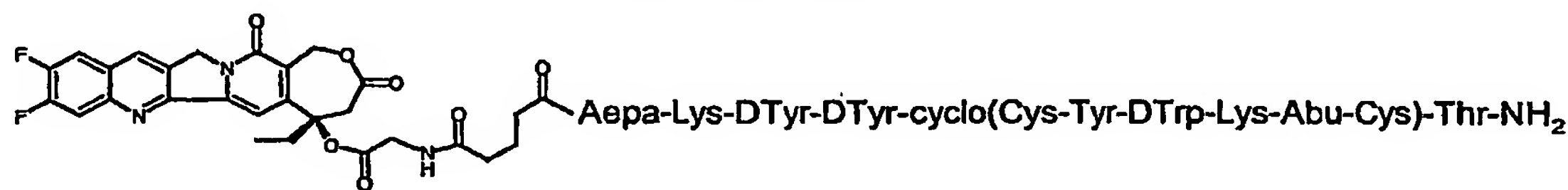
[0470] Example 62



[0471]

[0472] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=25%. Purity was 97% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2320.0 (in agreement with the calculated molecular weight of 2319.6).

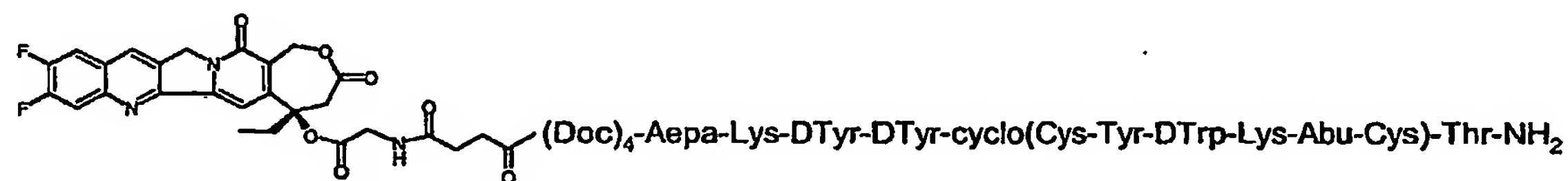
[0473] Example 63



[0474]

[0475] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=24%. Purity was 95% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2059.4 (in agreement with the calculated molecular weight of 2060.3).

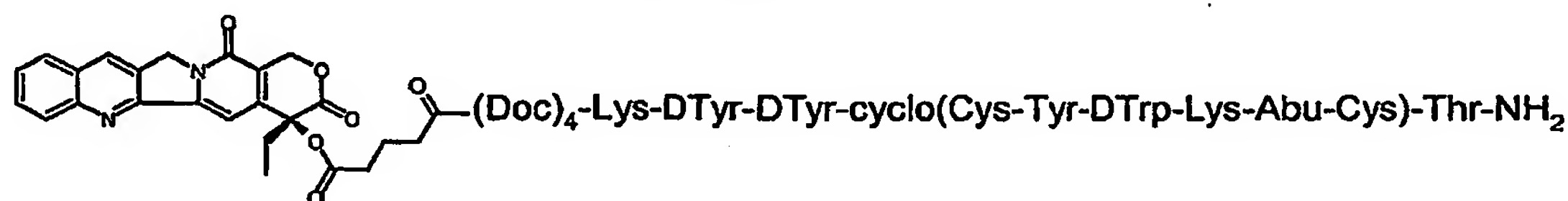
[0476] Example 64



[0477]

[0478] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=48. Purity was 99.9% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2626.0 (in agreement with the calculated molecular weight of 2626.9).

[0479] Example 65



[0480]

[0481] The title compound was synthesized substantially according to the procedure described in Example 19. Yield=10%. Purity was 98.9% based on analytical HPLC analysis. ESI MS analysis gave the molecular weight at 2365.0 (in agreement with the calculated molecular weight of 2365.0).

[0482] Example 66

[0483] H-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Aloc)-Abu-Cys(Trt)-Thr(tBu)-Rink-Amide-MBHA-Resin

[0484] The titled peptide was automatically synthesized on an Applied Biosystems (Foster City, CA) model 433A peptide synthesizer based on Fluorenylmethyloxycarbonyl (Fmoc) chemistry.

A Rink Amide MBHA resin (Nova Biochem, San Diego, CA) with substitution of 0.72 mmol/g was used. The Fmoc amino acids (AnaSpec, San Jose, CA) were used with the following side chain protection: Fmoc-Thr(tBu)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Lys(Aloc)-OH, Fmoc-DTrp(Boc)-OH, Fmoc-Tyr(OtBu)-OH, Fmoc-DPhe-OH, and Fmoc-Abu-OH. The synthesis was carried out on a 0.25 mmol scale. The Fmoc groups were removed by treatment with 20% piperidine in N-methylpyrrolidone (NMP) for 30 min. In each coupling step, the Fmoc amino acid (4 eq, 1 mmol) was first pre-activated by 0.45M 2-(1-H-benzotriazole-1-yl)-1,1,2,3-tetramethyluronium hexafluorophosphate / 1-hydroxy-benzotriazole (HBTU/HOBT) in DMF. This activated amino acid ester with 1ml of diisopropylethylamine (DIEA) and (NMP were added to the resin. The ABI 433A peptide synthesizer was programmed to perform the following reaction cycles: (1) washing with NMP, (2) removing Fmoc protecting group with 20% piperidine in NMP for 30 min, (3) washing with NMP, (4) coupling with pre-activated Fmoc amino acid for 1h. Single couplings were applied to the Cys(Trt)², Tyr(tBu)³, and DTrp(Boc)⁴. For all other amino acids double coupling was used. The resin was coupled successively according to the sequence. After peptide chain was assembled, the Fmoc was removed and washed completely by DMF and DCM.

[0485] Example 67

[0486] Fmoc-Aepa-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Aloc)-Abu-Cys(Trt)-Thr(tBu)-Rink-Amide-MBHA-Resin

[0487] The titled peptide was synthesized starting with the peptide from Example 66. The Fmoc-Aepa-OH (Neosystem Laboratoire, Gennevilliers, France. 1.5 eq, 0.75mmol) was pre-activated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU, 1.4 eq, 0.7 mmol) and 1-hydroxy-7-azabenzotriazole(HOAT, 1.4 eq, 0.7 mmol) in 2ml of DMF for 5 min. The above resin was transferred into a small reaction vessel and shaken with this activated ester of Fmoc-Aepa-OH and 1 ml of DIEA on a shaker for 2h. The resin was washed thoroughly with DMF and DCM.

[0488] Example 68

[0489] H-Doc-Doc-Doc-Doc-Aepa-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Aloc)-Abu-Cys(Trt)-Thr(tBu)-Rink-Amide-MBHA-Resin

[0490] The titled peptide was synthesized starting with the peptide from Example 68. The resin was washed with DMF and treated with 25% piperidine in DMF to remove Fmoc. The resin was mixed with a DMF solution of Fmoc-Doc-OH (Chem-Impex Internatoinal, Wood Dale, IL., 1.5 eq, 0.75 mmol) N, N-diisopropylcarbodiimide (DIC, 1.5 eq, 0.75 mmol), and HOBT (1.5 eq, 0.75 mmol) for 2h. The second through fourth Fmoc-Doc-OH were coupled to the resin using the

same procedure as described in coupling of the first Fmoc-Doc-OH. The process was repeated until the assembly of peptide chain was completed.

[0491] The final Fmoc was removed with 25% piperidine in DMF. The resin was washed with DMF and DCM.

[0492] Example 69

[0493] H-Doc-Doc-Doc-Doc-Aepa- DPhe-c(Cys-Tyr-DTrp-Lys(Aloc)-Abu-Cys)-Thr-NH₂

[0494] The peptide was cleaved from the Resin using 19 mL of TFA (Trifluoroacetic Acid, Halocarbon Products Corp. River Edge, NJ), 1.6 mL of TIS (Triisopropylsilane, Aldrich) and 1.7 mL of water for 2 hours. The resin was filtered and the peptide precipitated by pouring into ether. Dissolve the precipitate in 150 mL of 5% acetic acid and 30 mL of acetonitrile. I₂ (20 mg/mL in MeOH) was added dropwise till there was a persistent red color. The flask was placed in a bath of hot tap water and stirred for 2 hours. The reaction was quenched using 10% Na₂SSO₃. The peptide was purified using a Phenomenex C₁₈ column with a gradient 5-60% CH₃CN where Buffer A is 0.1%TFA in water and Buffer B is 0.1% TFA in CH₃CN over 60 minutes. The fractions containing product were freeze dried to give 186 mg(40% yield) of white powder. MS (Electro Spray): 1722.2

[0495] Example 70.

[0496] H-Doc-Doc-Doc-Aepa-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Aloc)-Abu-Cys(Trt)-Thr(tBu)-Rink-Amide-MBHA-Resin

[0497] The titled peptide was synthesized starting with the peptide from Example 67. The resin was washed with DMF and treated with 25% piperidine in DMF to remove Fmoc. The resin was mixed with a DMF solution of Fmoc-Doc-OH (Chem-Impex International, Wood Dale, IL., 1.5 eq, 0.75 mmol) N, N-diisopropylcarbodiimide (DIC, 1.5 eq, 0.75 mmol), and HOBt (1.5 eq, 0.75 mmol) for 2h. The second and third Fmoc-Doc-OH were coupled to the resin using the same procedure as described in coupling of the first Fmoc-Doc-OH. The process was repeated until the assembly of peptide chain was completed. The final Fmoc was removed with 25% piperidine in DMF. The resin was washed with DMF and DCM.

[0498] Example 71

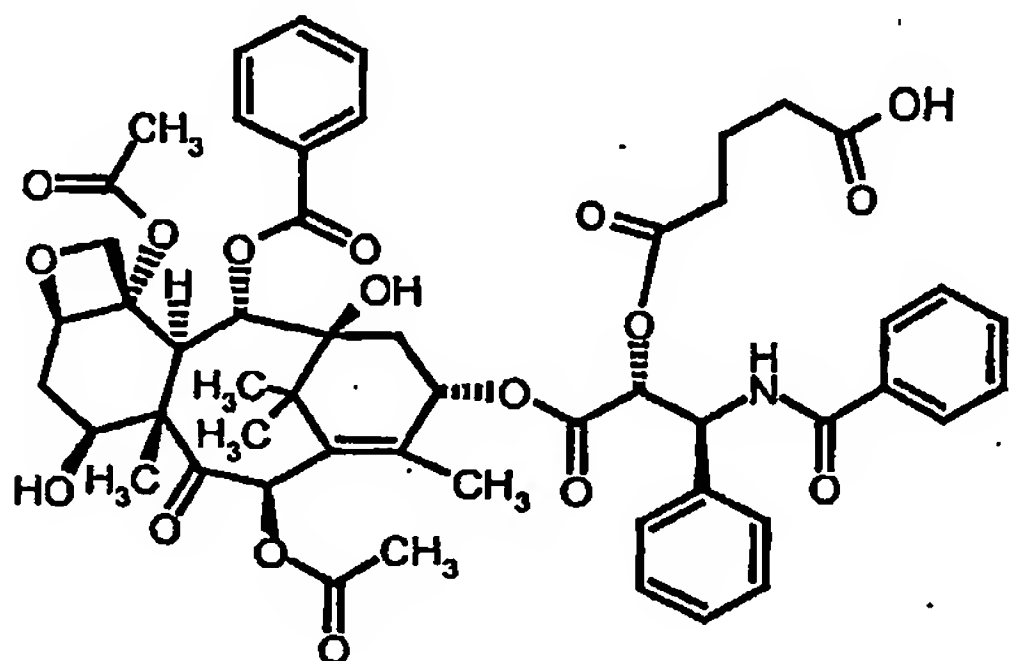
[0499] H-Doc-Doc-Doc-Aepa- DPhe-c(Cys-Tyr-DTrp-Lys(Aloc)-Abu-Cys)-Thr-NH₂

[0500] The peptide was cleaved from the Resin using 19 mL of TFA (Trifluoroacetic Acid, Halocarbon Products Corp. River Edge, NJ), 1.6 mL of TIS (Triisopropylsilane, Aldrich) and 1.7 mL of water for 2 hours. The resin was filtered and the peptide precipitated by pouring into ether. Dissolve the precipitate in 150 mL of 5% acetic acid and 30 mL of acetonitrile. I₂ (20 mg/mL of MeOH) was added dropwise till there was a persistent red color. The flask was placed

in a bath of hot tap water and stirred for 2 hours. The reaction was quenched using 10% Na_2SSO_3 . The peptide was purified using a Phenomenex C_{18} column with a gradient 5-60% CH_3CN where Buffer A is 0.1%TFA in water and Buffer B is 0.1%TFA in CH_3CN over 60 minutes. The fractions containing product were freeze dried to give 180mg(42% yield) of white powder. MS (Electro Spray):1722.2,

[0501] Example 72

[0502] Paclitaxel-2'-glutarate

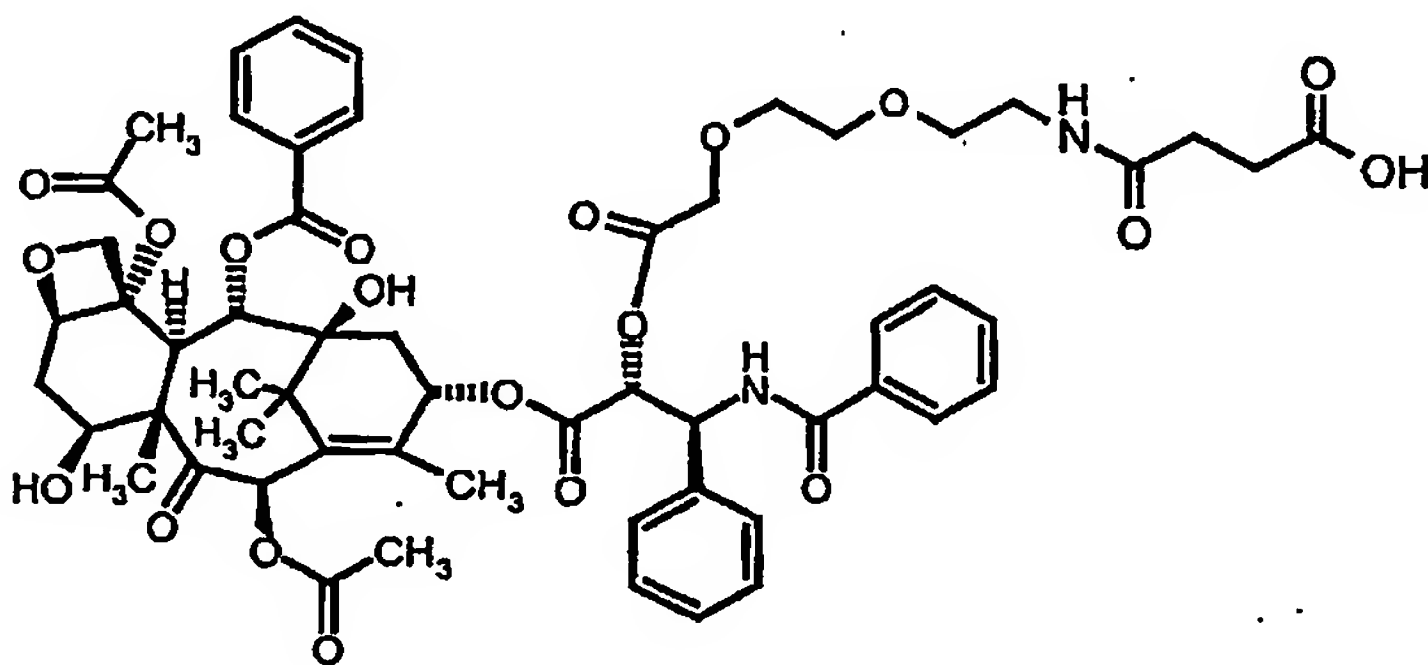


[0503]

[0504] To a solution of Paclitaxel (HandeTech USA, Inc, Houston, Texas, 1g., 1.17 mmol) in 10 mL of pyridine was added glutaric anhydride (Aldrich, 1.6 g, 14.1 mmol, 12 eq.). The resulting solution was stirred at room temperature for 4 hours and then evaporated at reduced pressure. 20 mL of water was added. The sticky solid was collected by filtration. Recrystallization from acetone/water gave 0.842 g of white solid, 0.869mmole, 74% yield. MS (Electro Spray): 969.0.

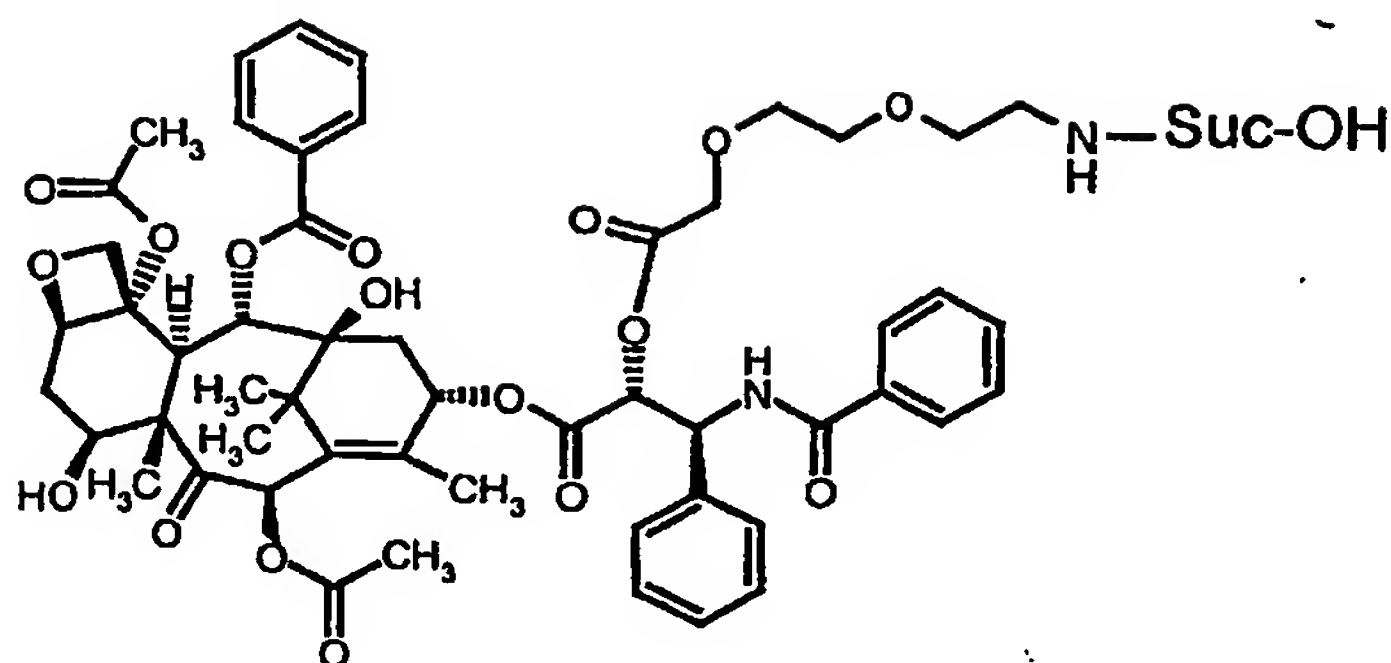
[0505] Example 73

[0506] Paclitaxel-2'-Doc-Suc-OH



[0507]

[0508] or



[0509]

[0510] To a solution of paclitaxel (1 g., 1.17 mmol) and the Boc-Doc-OH (0.31g., 1.17 mmol) in 25 mL of DCM was added DIC (0.241 mL, 1.54 mmol) followed by DMAP (50 mg, 0.4 mmol). The resulting solution was stirred at room temperature for 4 hours. The solution was washed with 3 X 10% citric acid, 3 X saturated NaHCO₃, 1 x saturated NaCl and dried over MgSO₄, filtered and evaporated. The resulting residue was dissolved in EtOAc and then precipitated with hexane. The product was collected by filtration and dried under reduced pressure. Solid (1.19 g, 1.08 mmol) was obtained. Yield was 92%. MS (Electro Spray): m/e=1099.7(+1), Purity was 95% by HPLC. The resulting Boc-Doc-paclitaxel (1.19 g, 1.08 mmol) was dissolved in 20 mL of formic acid, stirred for 30 minutes and then evaporated. The product was dissolved in 15 mL of pyridine. To the solution was added succinic anhydride (1.29 g, 13 mmol). The mixture was stirred at room temperature overnight. Pyridine was removed by evaporation under reduced pressure. The residue was triturated with water and collected (0.99 g, 0.91mmole, 84% yield). MS (Electro Spray) gave 1099.4(+1), 1121.6 (Na+1). Purity was 75% by HPLC.

[0511] Example 74

[0512] Paclitaxel-2'-glutaryl-Doc-Doc-Doc-Doc-Aepa-DPhe-c(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

[0513] To a DMF (10 mL) solution of the peptide (125 mg, 0.067 mmol) from Example 69 was added paclitaxel-2'-Glut-OH (Example 72, 65 mg, 0.067 mmol), HOBt (20 mg, 0.147 mmol), BOP (29 mg, 0.067mmol) and DIEA (8 eq., 93 µL). The solution was stirred overnight and then evaporated under reduced pressure. The residue was dissolved in minimal MeOH and precipitated with ether. A solid was obtained (108 mg, 0.04 mmol). Yield was 60% y. MS (Electro Spray) showed 1409.5(+2). To remove the Alloc from the Lys, the peptide was dissolved in DCM/THF (anhydrous, 15mL/5mL). To is were added glacial acetic acid (15 µL, 5 eq.), Pd(PPh₃)₄ (12 mg, 0.3 eq.) and Bu₃SnH(2x31 µL, 3eq) at 0 °C. After stirring 1 hour, the solution was quenched using 0.5M HCl in ether (0.7mL, 10 eq.). The peptide was precipitated with ether. The crude peptide was purified on a PLRP-S column (Polymer Labs, 100A, 8µ) using

a gradient of 5-90% over 1 hour where solvent A was 5%MeOH in water and solvent B was CH₃CN. Pure fractions were combined and lyophilized, yielding 42 mg of the peptide. MS (Electro Spray) gave 2731.4 (in agreement with the calculated molecular weight of 2732.1). Purity was 99.9% based on HPLC analysis.

[0514] Example 75

[0515] Paclitaxel-2'-Doc-Suc-Doc-Doc-Doc-Aepa-DPhe-c(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂

[0516] To a DMF (10ml) solution of the peptide (200 mg, 0.12 mmol) from Example 71 was added paclitaxel-2'-Doc-Suc-OH (Example 73, 140 mg, 0.128 mmol), HOBT (39 mg, 0.281 mmol), BOP (74 mg, 0.166 mmol) and DIEA (8 eq., 177 μ L). The solution was stirred overnight and evaporated under reduced pressure. A solid was obtained (355 mg, 0.126 mmol).

[0517] To remove the Alloc from the Lys, the product was dissolved in DCM/THF (anhydrous, 15mL/5mL). To it were added glacial acetic acid (19 μ L, 5 eq.), Pd(PPh₃)₄ (12 mg, 0.3 eq.) and Bu₃SnH (2x54 μ L, 3eq) at 0 °C. The solution was stirred for 1hour and then quenched using 0.5M HCl in ether (0.7 mL, 10 eq.). The product was precipitated with ether. Purify was done on a PLRP-S column (Polymer Labs, 100A, 8 μ) using a gradient of 5-90% over 1 hour where solvent A was 5% MeOH in water and solvent B was CH₃CN. Pure fractions were combined and lyophilized. MS (Electro Spray) gave 2717.3 (in agreement with the calculated molecular weight of 2718.1). Purity was 99.9% based on HPLC analysis

[0518] Biological Assays

[0519] Stable Expression of hsst Receptor Subtypes

[0520] The complete coding sequences of genomic fragments of the hsst1,2,3,4 receptor genes and a cDNA clone for hsst5 were subcloned into the mammalian expression vector pCMV.

Clonal cell lines stably expressing the hsst1-5 receptors were obtained by transfection into CHO-K1 cells (ATCC) using the calcium phosphate co-precipitation method (Ausabel et al, 1987). The plasmid pRSV-neo (ATCC) was included as a selectable marker. Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Gibco), ring cloned, and expanded into culture.

[0521] Radioligand Binding Assays

[0522] Membranes for in vitro receptor binding assays were obtained by homogenizing (Polytron setting 6, 15 sec) the CHO-K1 cells, expressing the hsst receptor subtypes, in ice-cold 50 mM Tris-HCl and centrifuging twice at 39,000 g (10 min), with an intermediate resuspension in fresh buffer. The final pellets were resuspended in 10 mM Tris-HCl for assay. For the hsst1,3,4, assays, aliquots of the membrane preparations were incubated (90 min/25 °C with 0.05 nM [125I-Tyr11]SRIF-14 in 50 mM HEPES (pH 7.4) containing BSA (0.2%); MgCl₂ (5 mM).

The final assay volume was 0.3 ml. For the hsst2,5 assay, [¹²⁵I]-[4-(2-hydroxyethyl)]-1-piperazinylacetyl-DPhe-c(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂ (0.05 nM) and [¹²⁵I]-DPhe-c(Cys-Tyr-DTrp-Lys-Val-Cys)-Thr-NH₂ were employed as the radioligands, respectively, and the incubation times were 90 min/25 °C. The incubations were terminated by rapid filtration through GF/C filters (pre-soaked in 0.3% polyethylenimine) using a Brandel filtration manifold. Each tube and filter were then washed three times with 5-ml aliquots of ice-cold buffer. Specific binding was defined as the total radioligand bound minus that bound in the presence of 1000 nM SRIF-14(hsst1,3,4,5), or 1000 nM DPhe-c(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂ for hsst2.

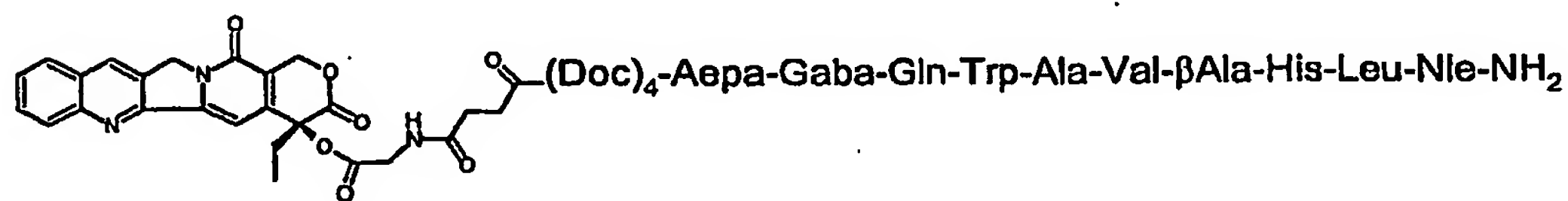
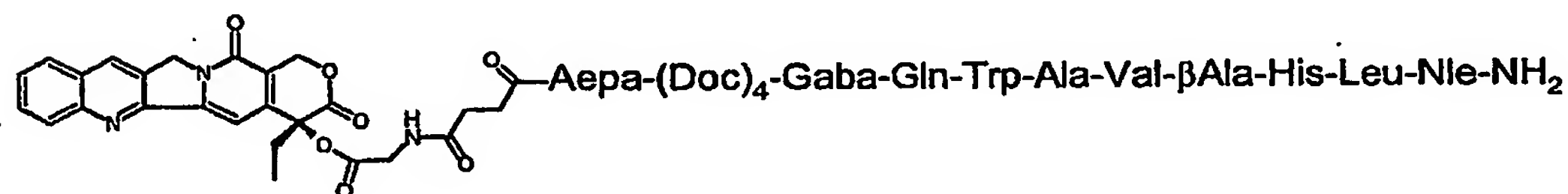
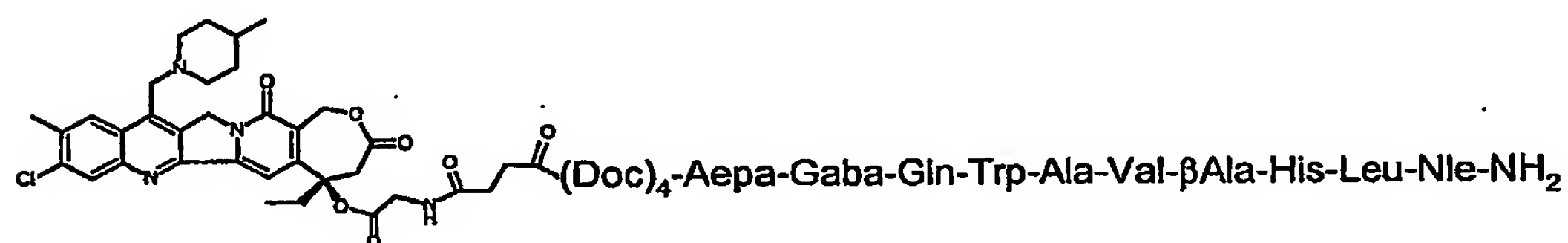
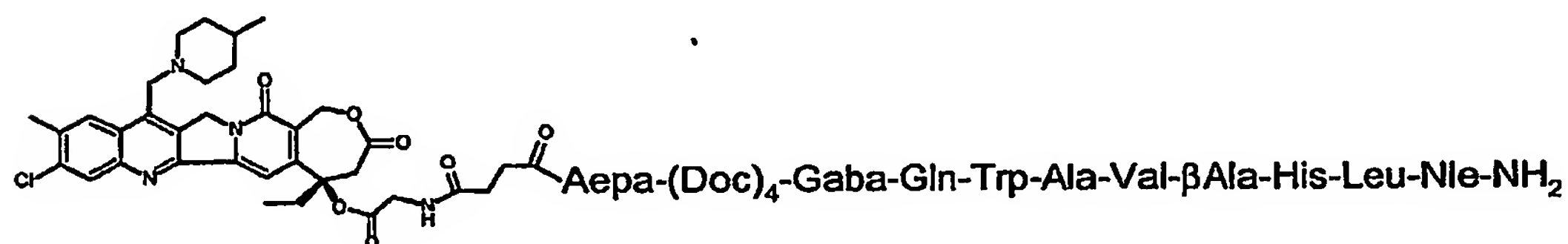
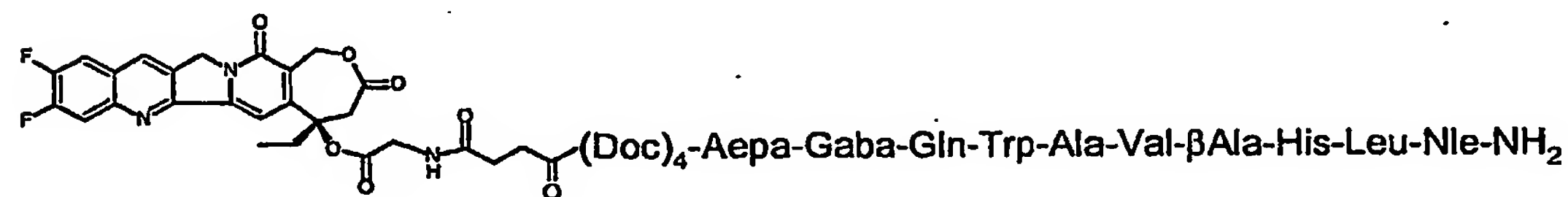
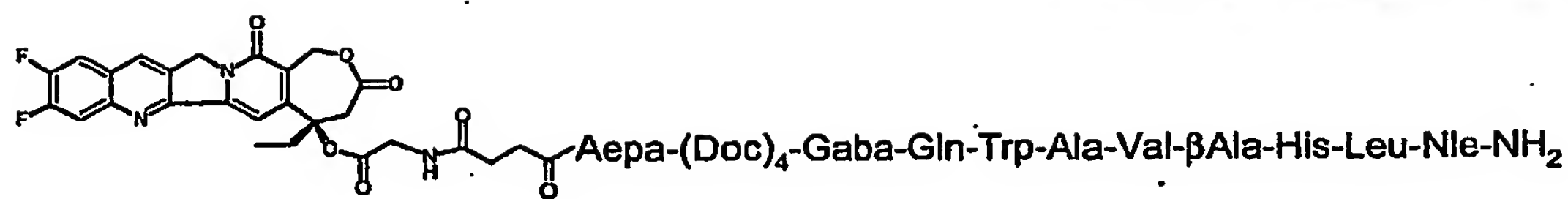
[0523] In Vitro Growth Assays

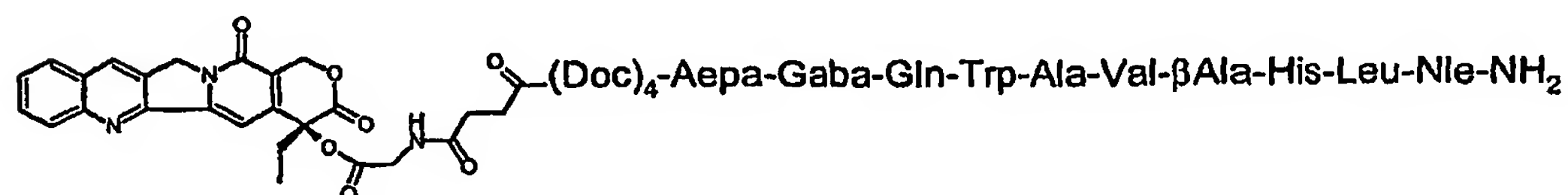
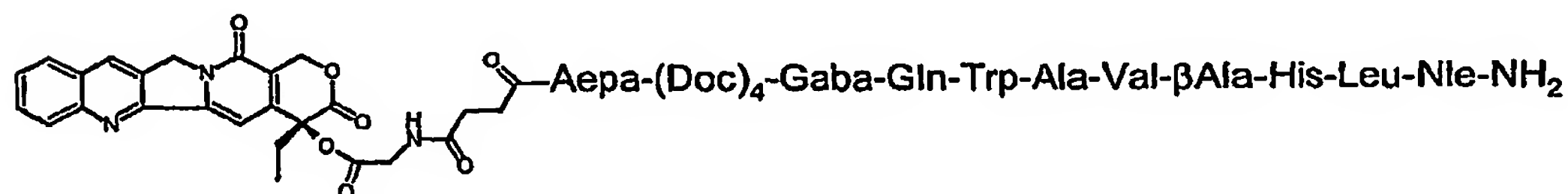
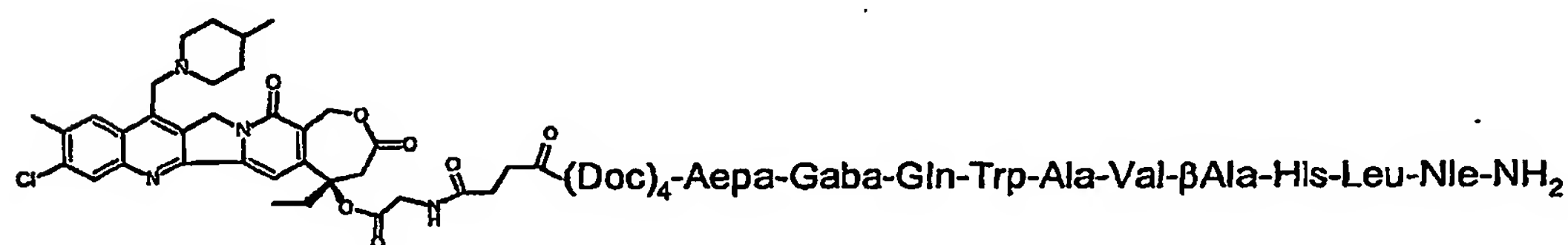
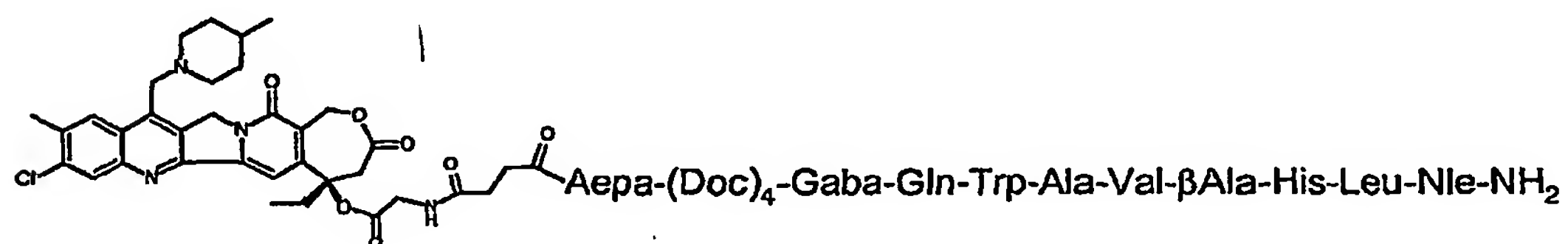
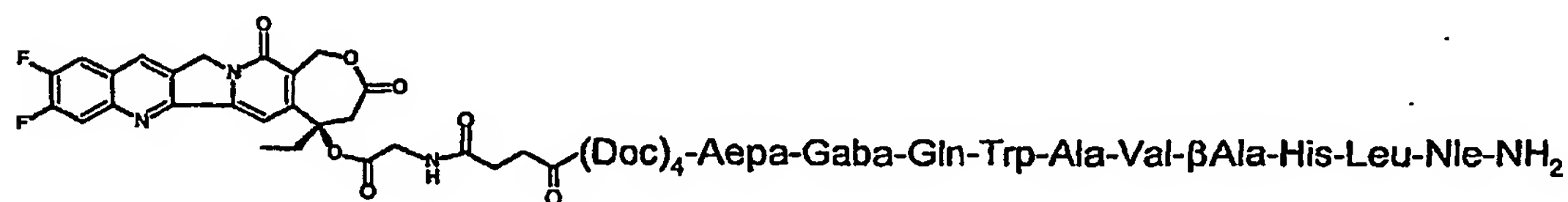
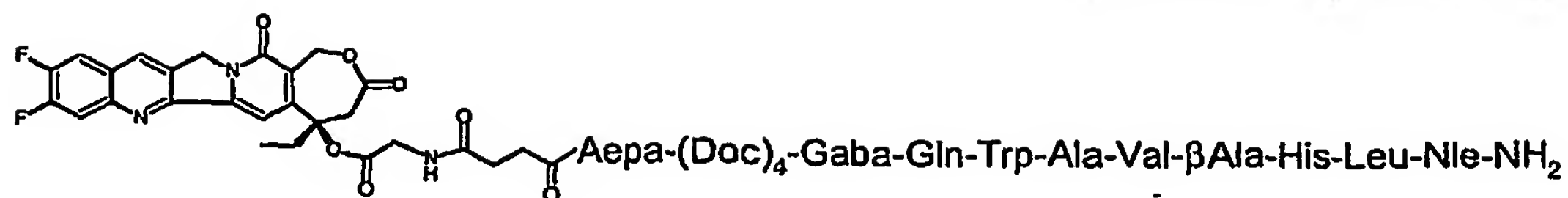
[0524] For the in vitro proliferation assays, cultured CHO-K1 cells, or CHO-K1 cells expressing the hsst2 receptor were seeded into plastic 24-well plates in RPMI 1640 Medium (DMEM) containing 10% fetal bovine serum (FBS) at a density of approximately 10⁴ cells/well/1.0 ml. The test peptides were added at the desired concentration and maintained in culture (5% CO₂, 37°C, humidified air) for one to three days. For counting the cells were rinsed with serum-free RPMI media, trypsinized,, resuspended RPMI 1640 (+10% FBS) and counted with a with a Coulter Counter at 1:20 dilution.

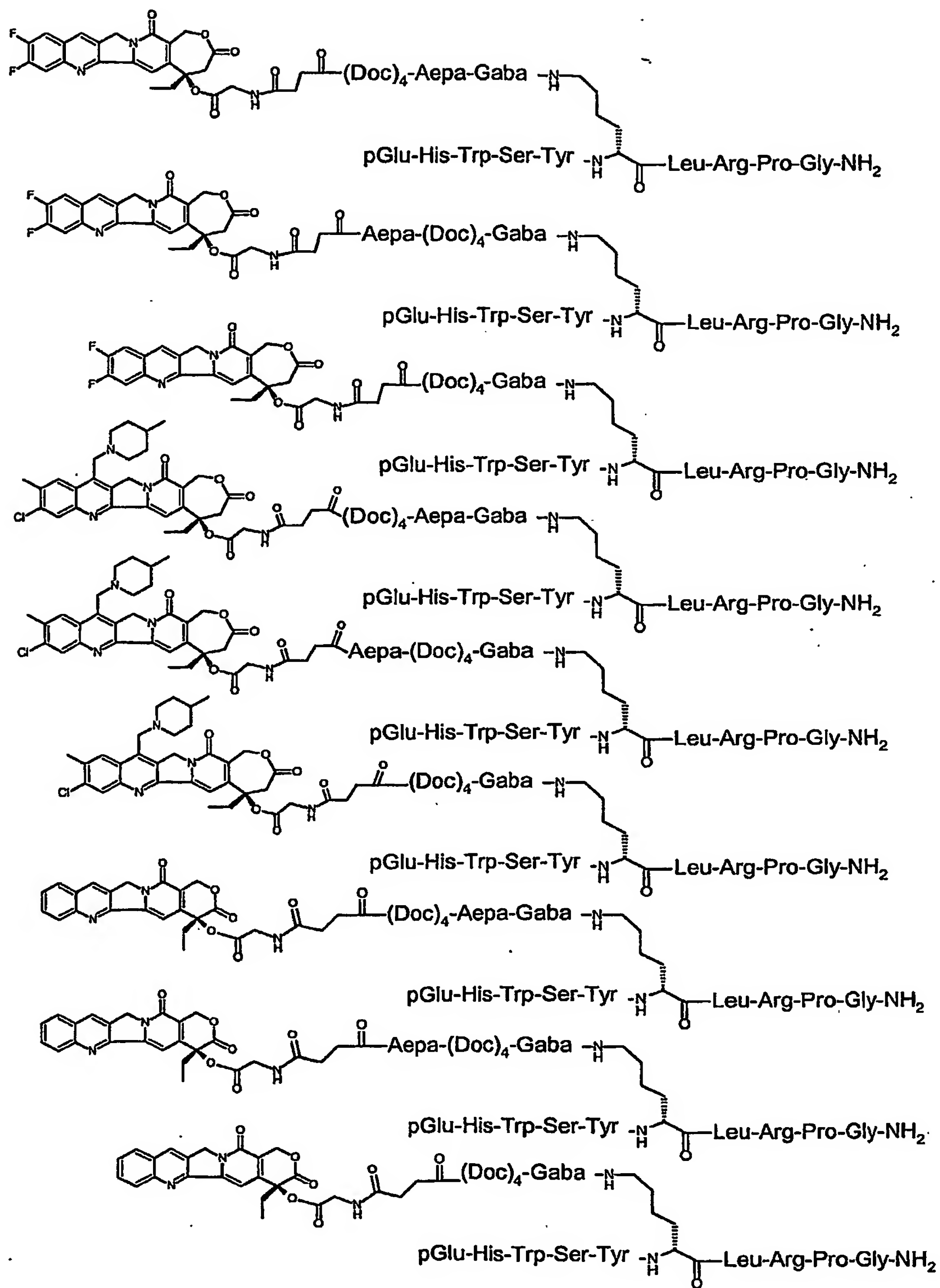
[0525] It is to be understood that while the invention has been described in conjunction with the examples and the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention defined by the appended claims. Other aspects, advantages, and modifications are within the claims.

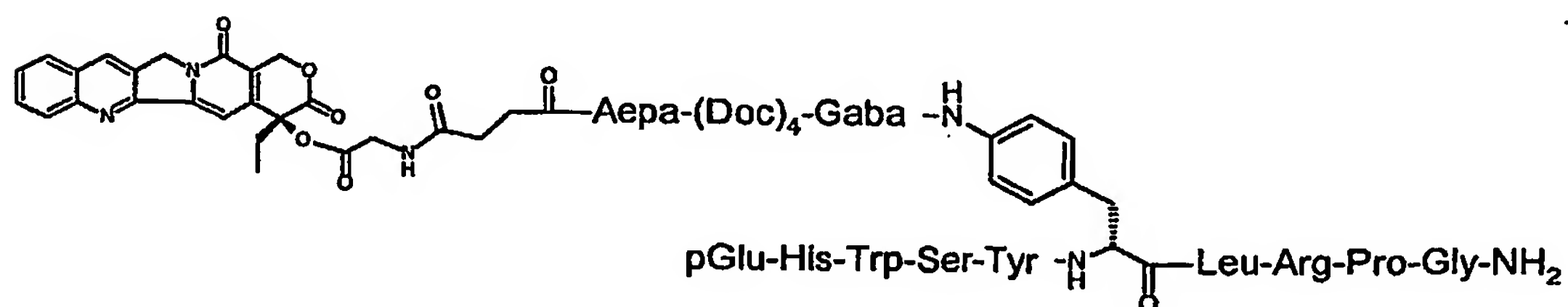
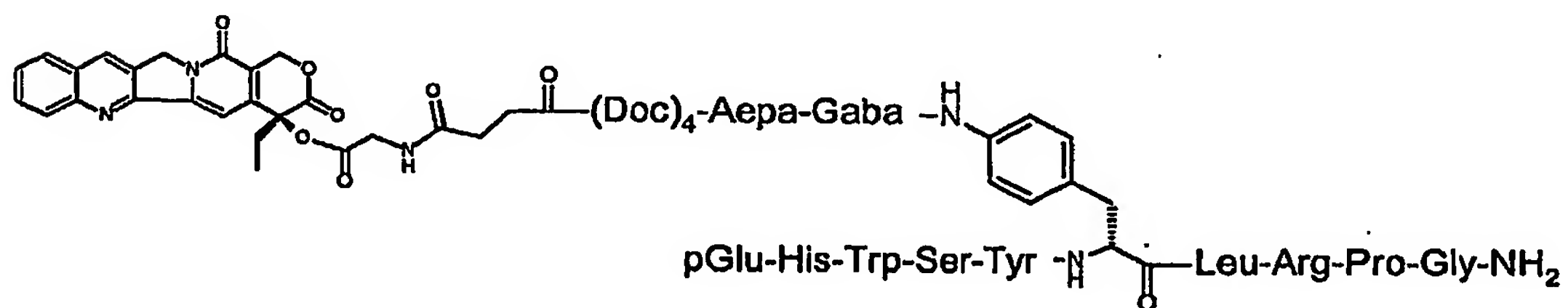
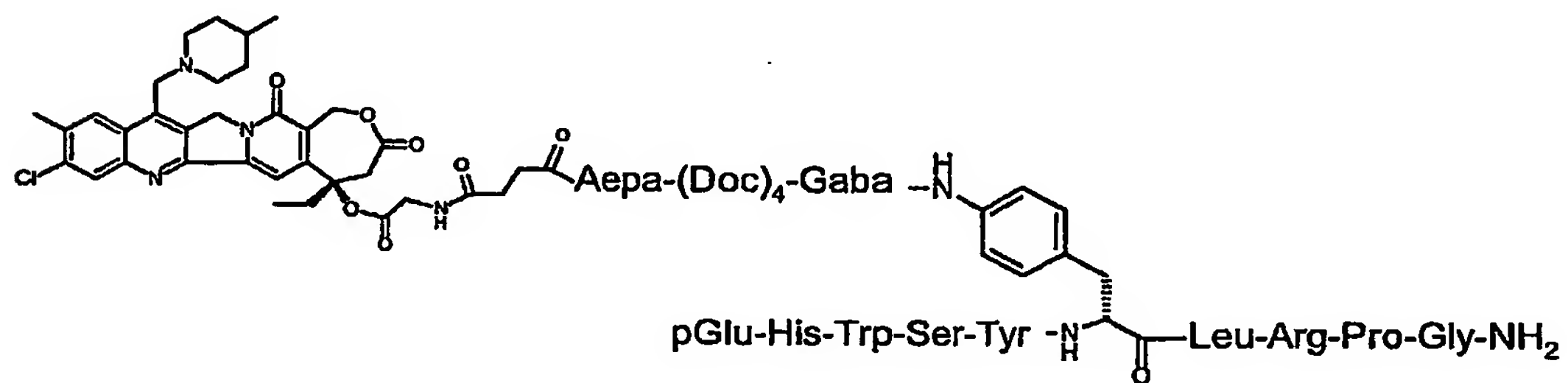
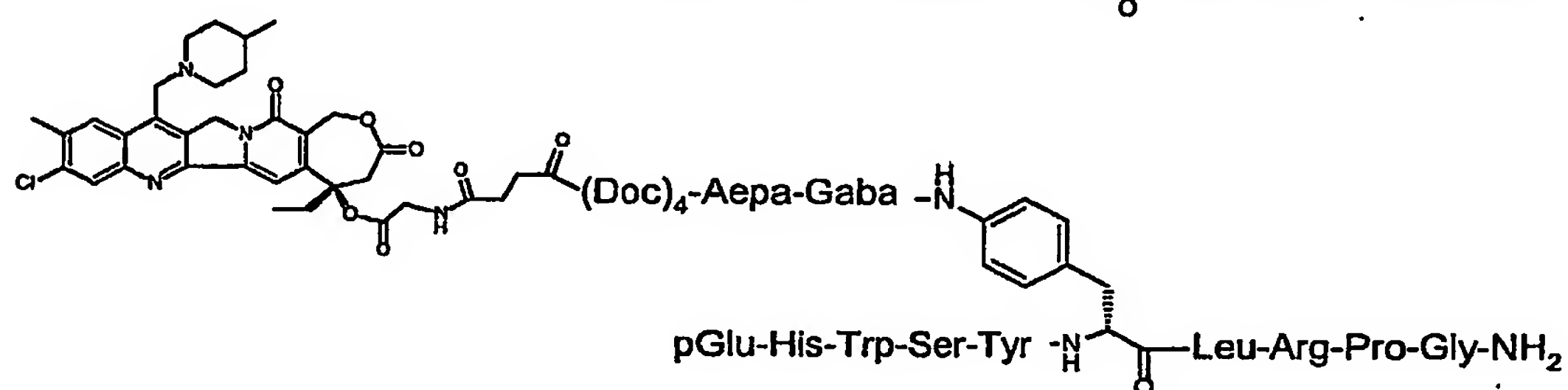
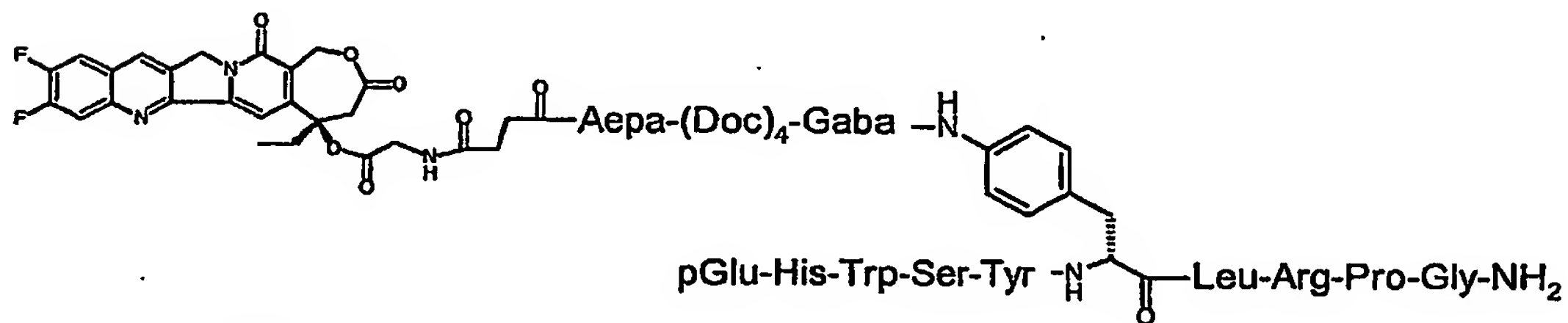
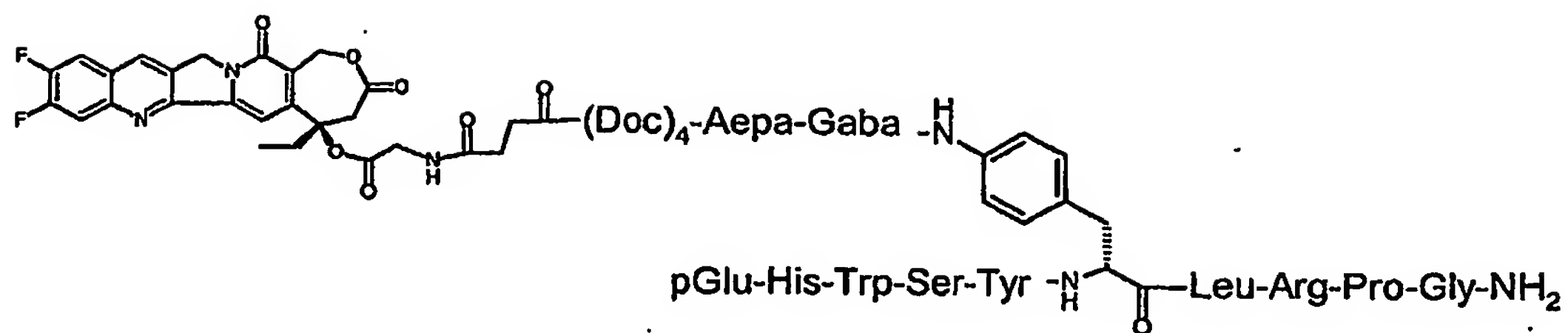
[0526] We claim:

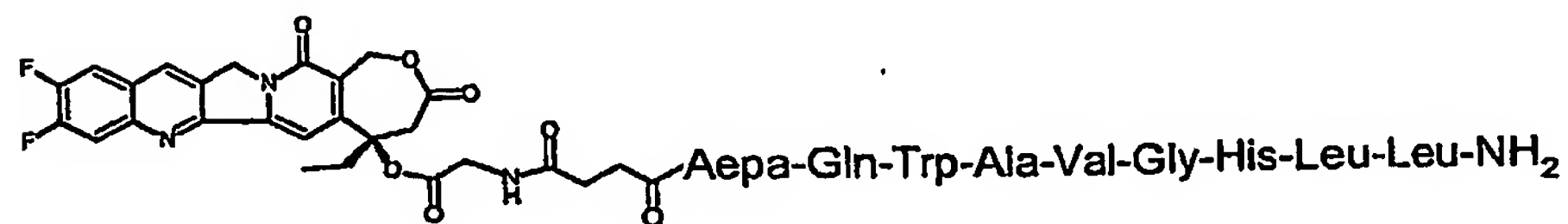
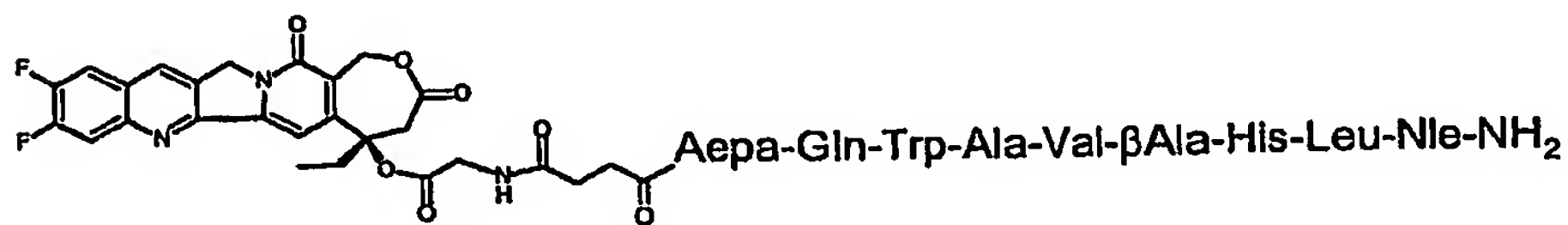
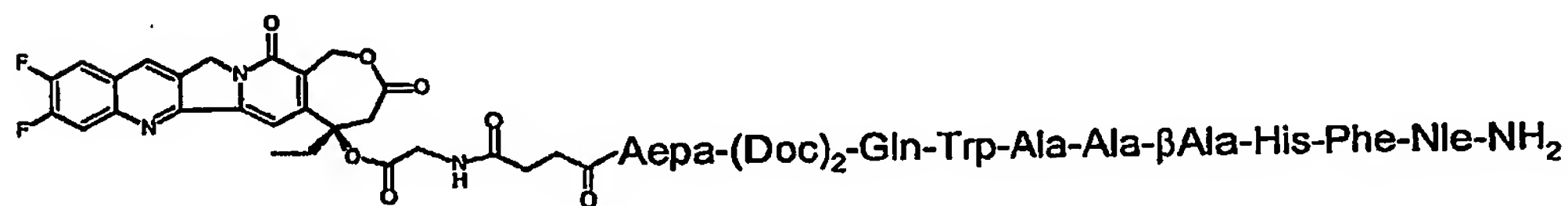
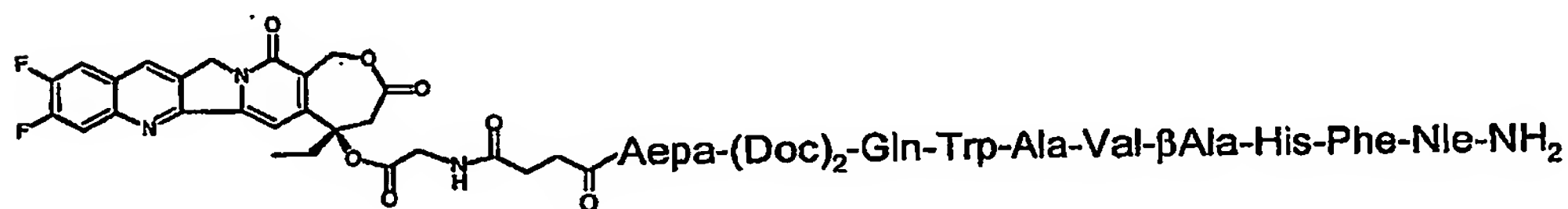
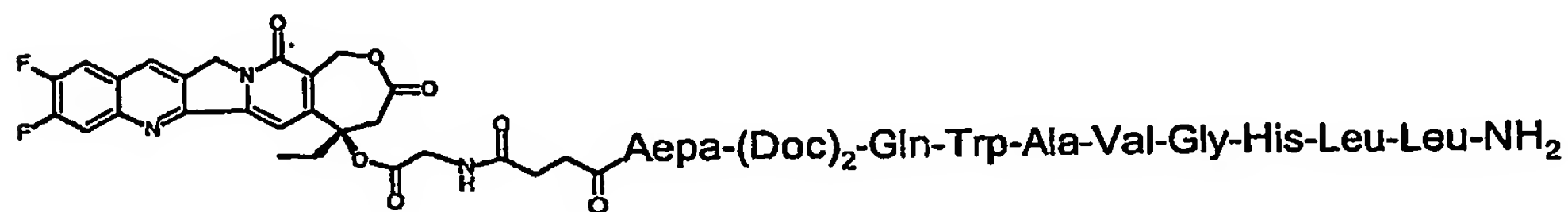
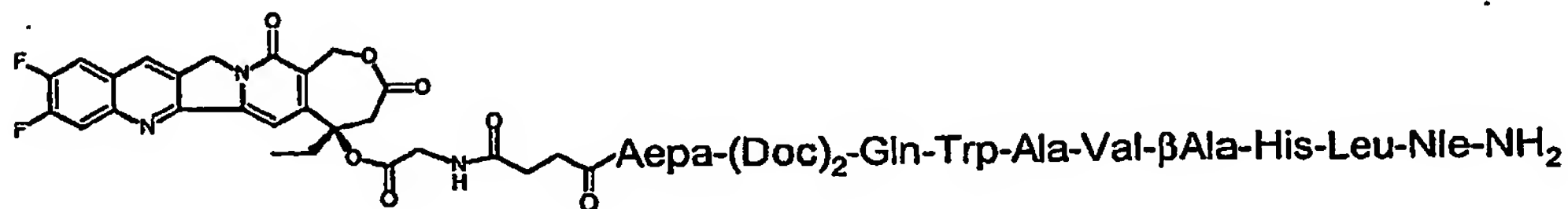
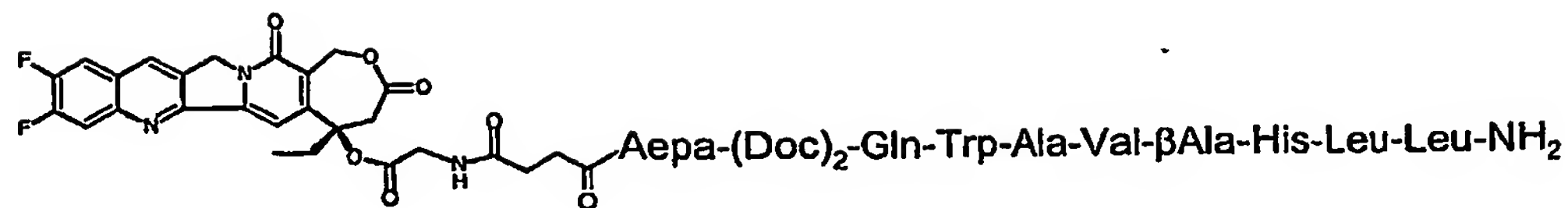
Appendix A

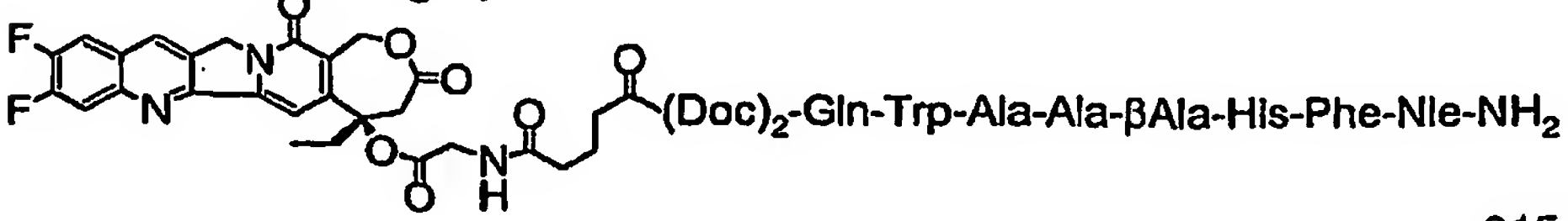
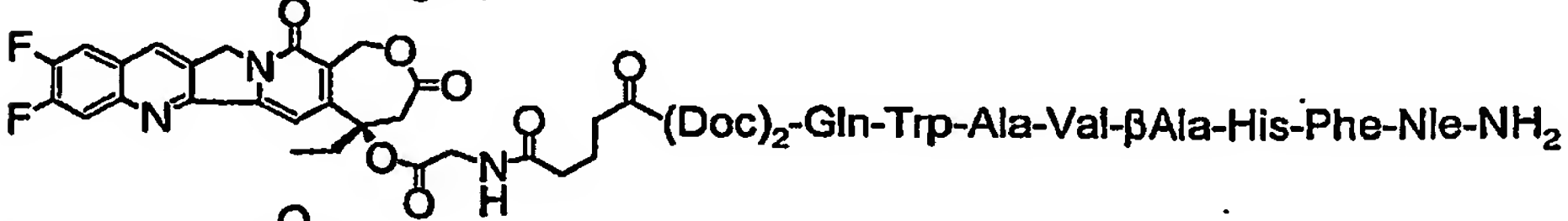
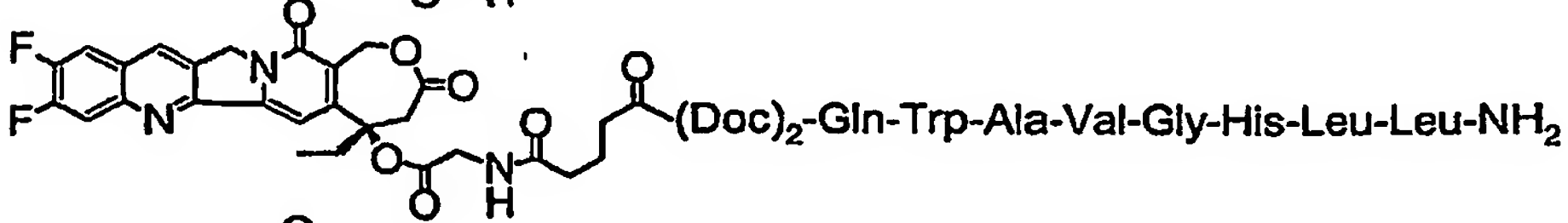
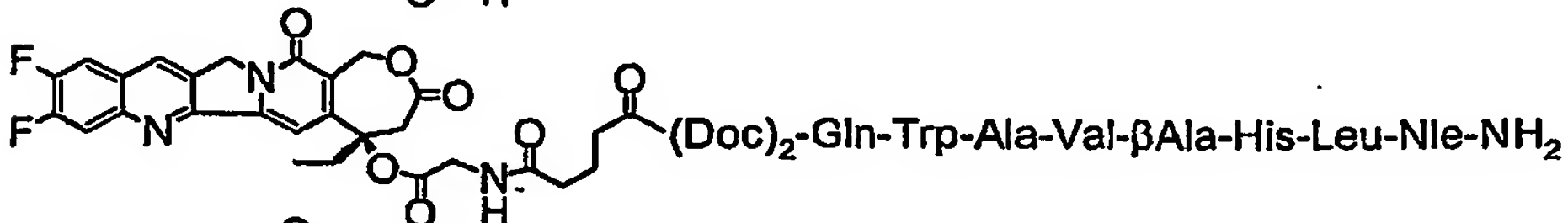
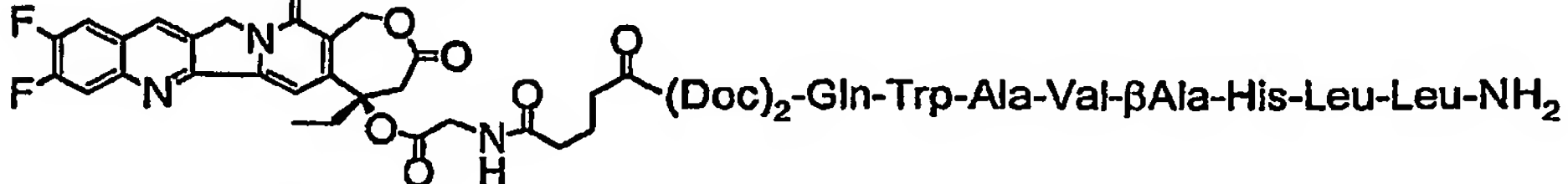
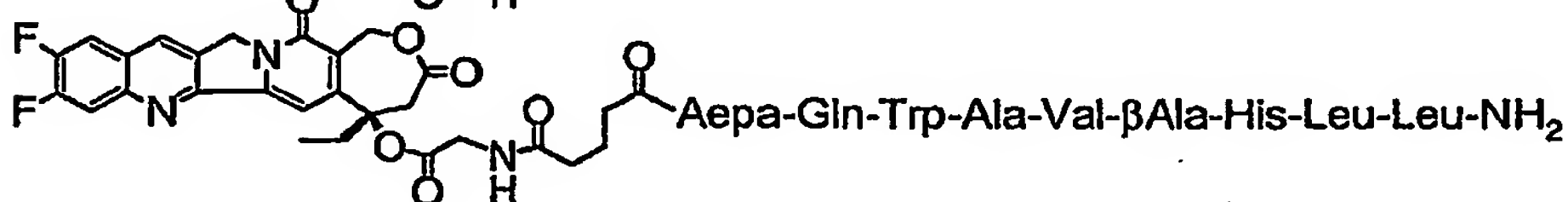
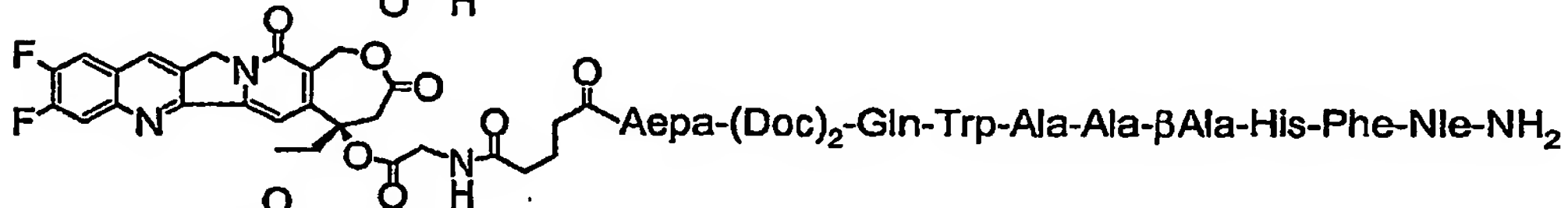
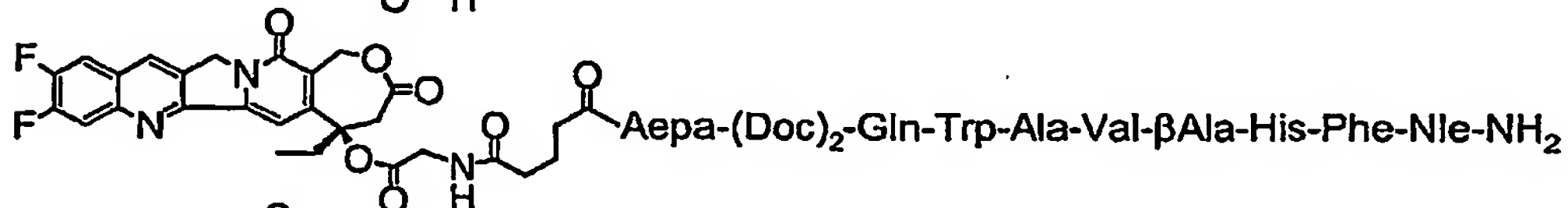
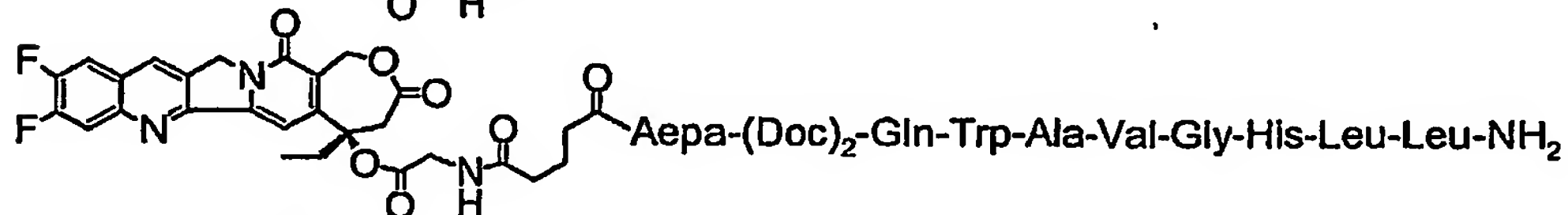
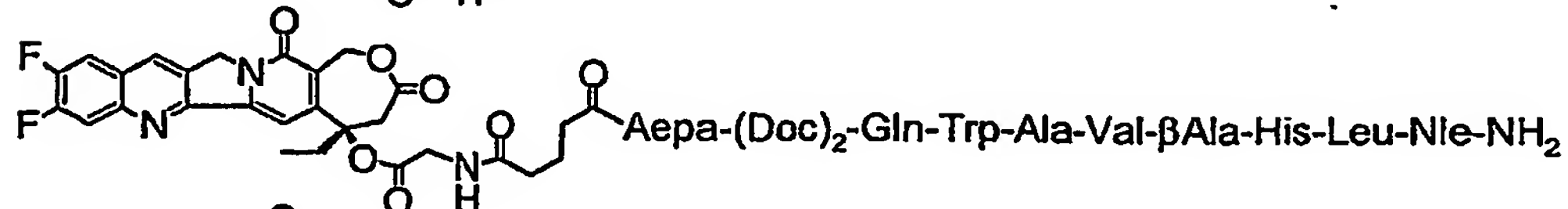
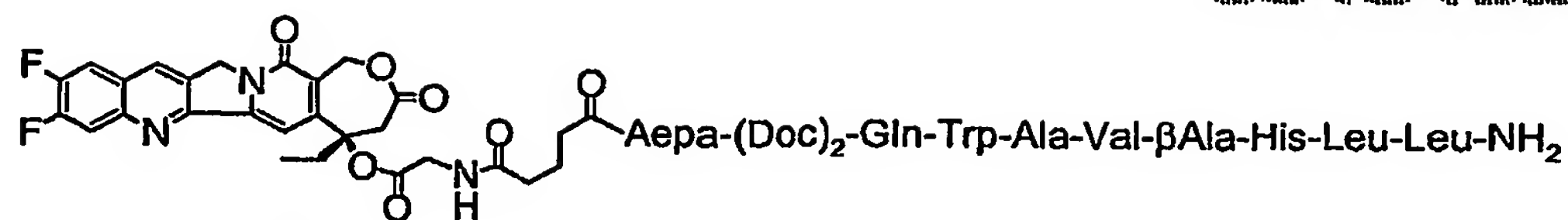


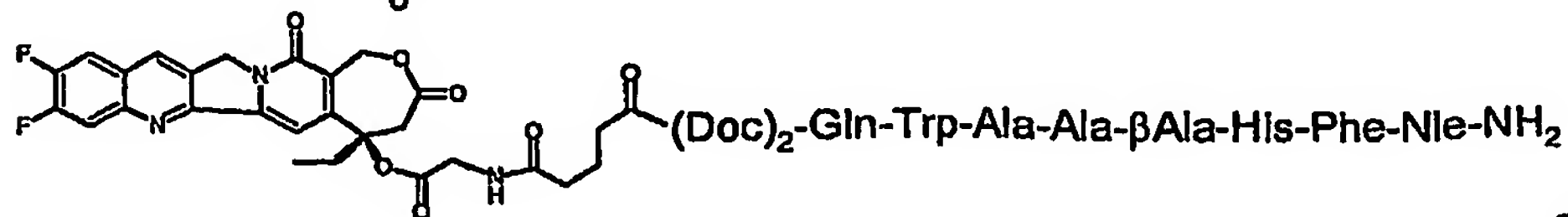
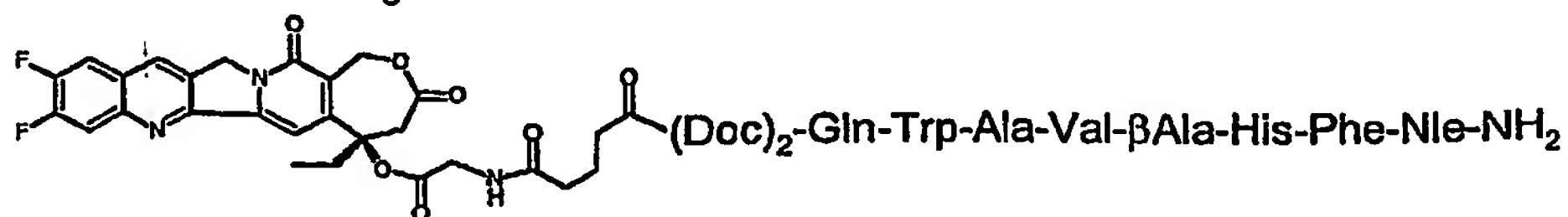
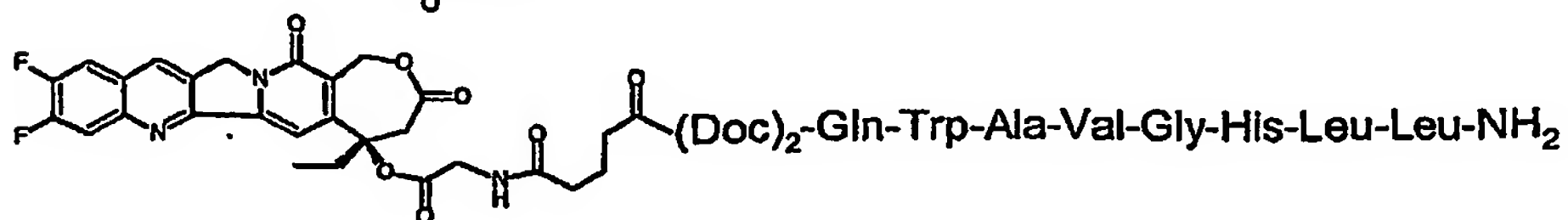
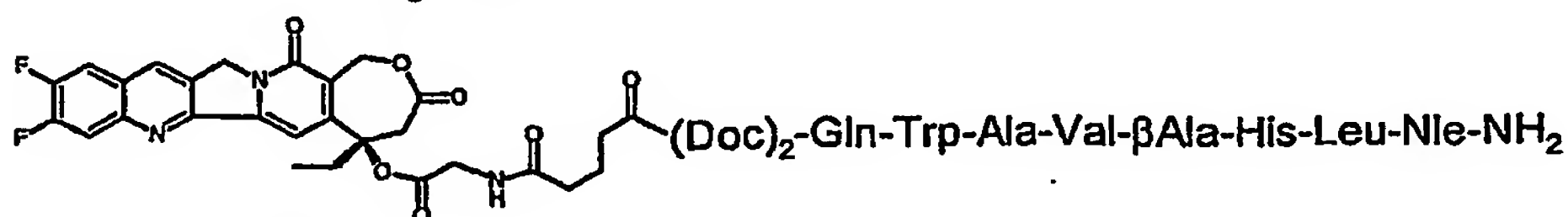
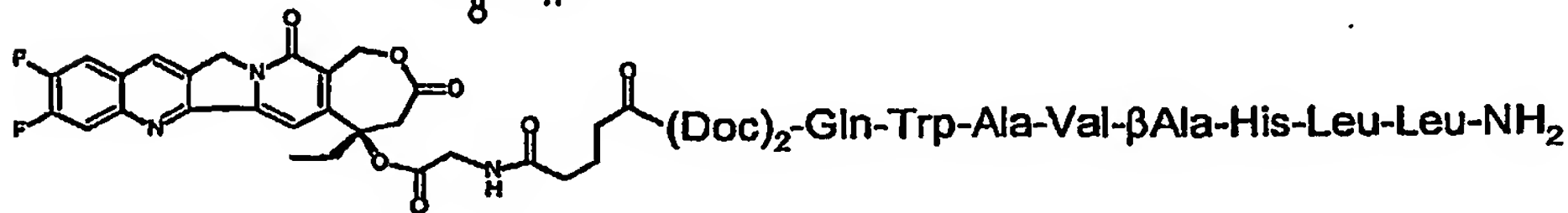
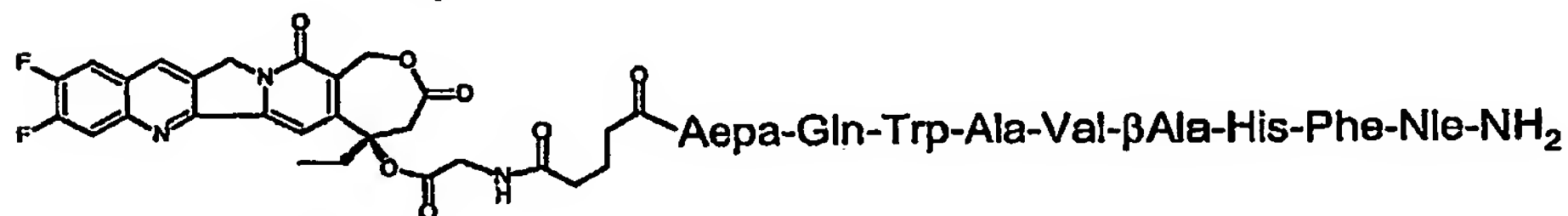
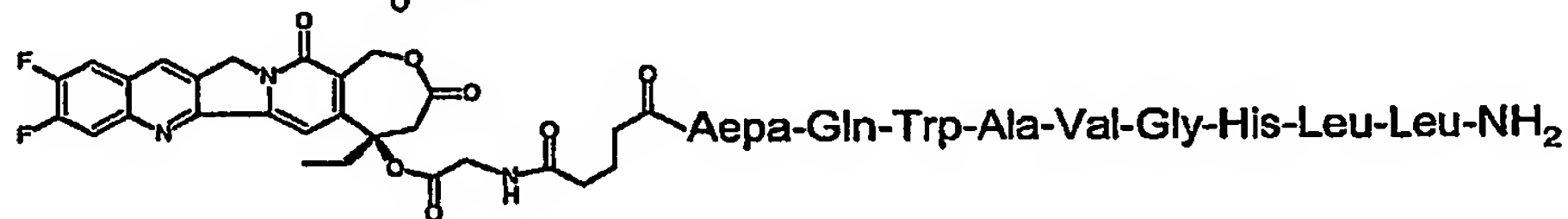
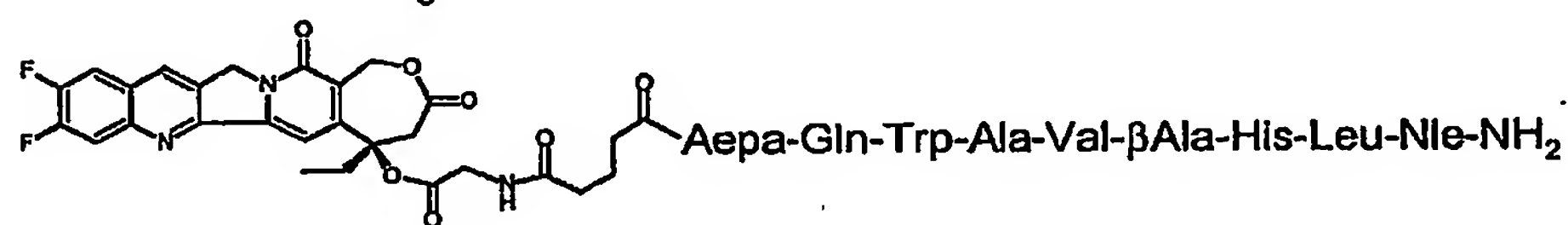
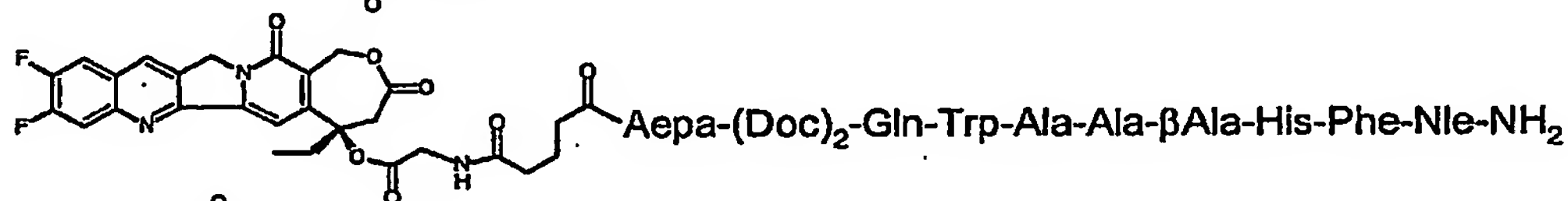
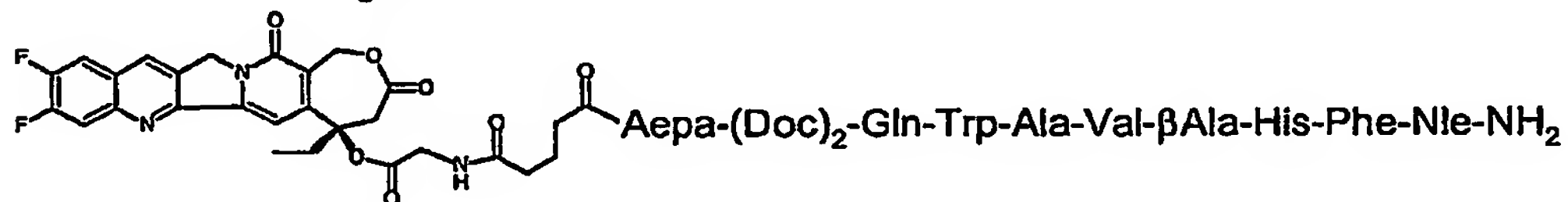
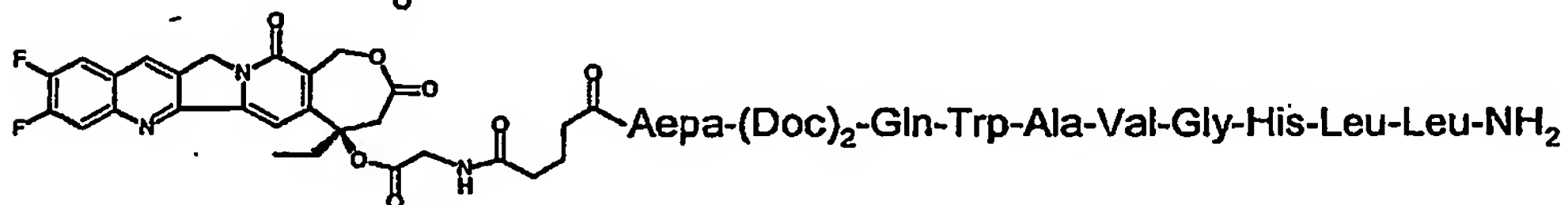
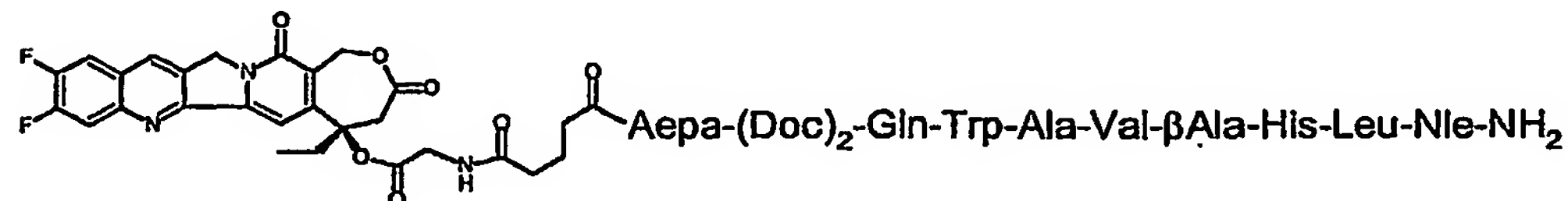
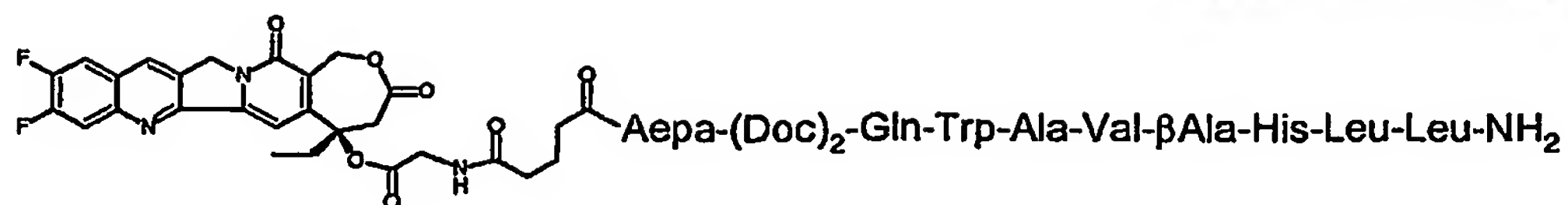


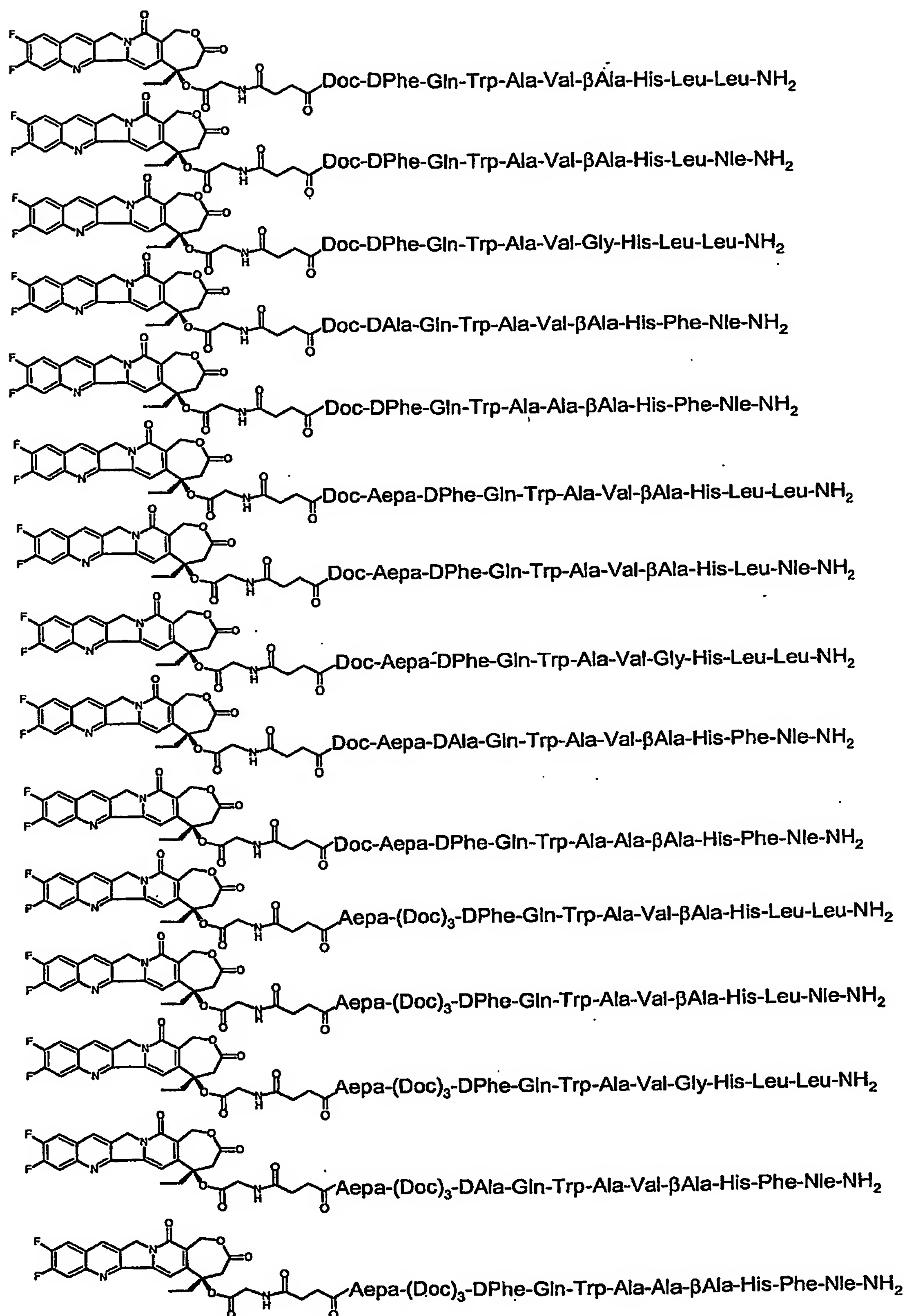


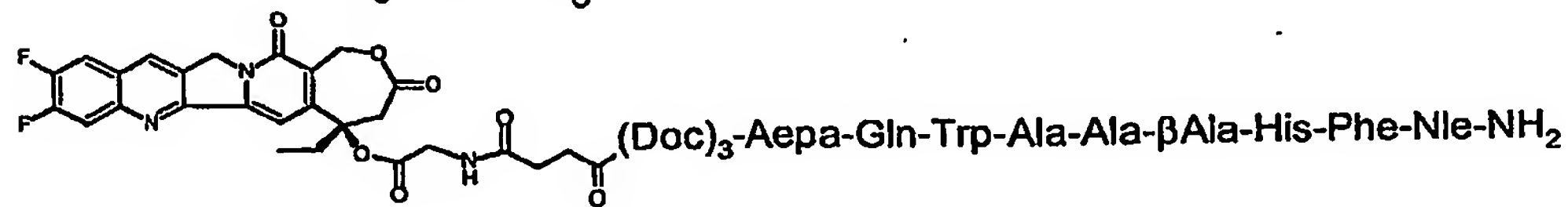
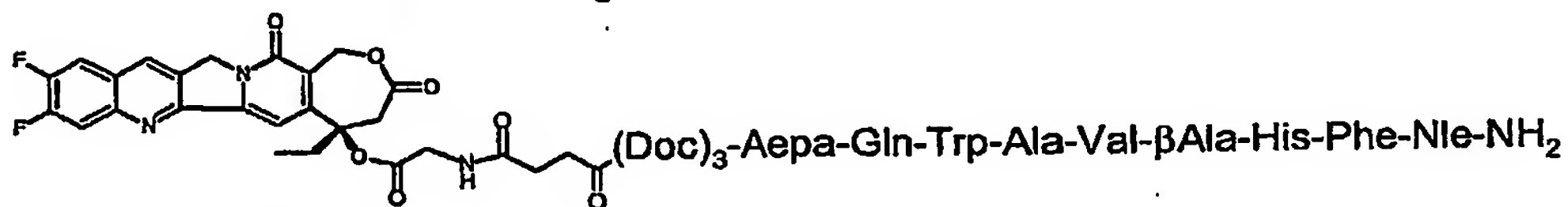
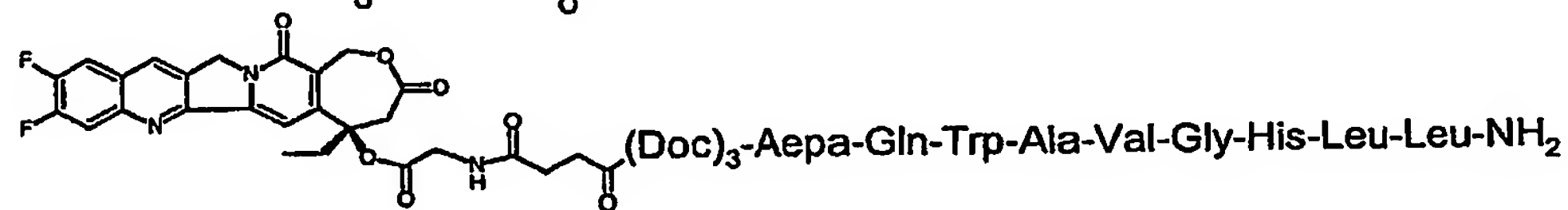
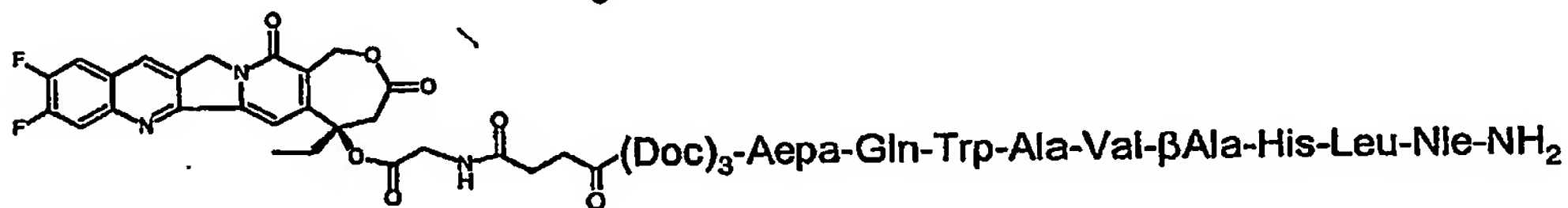
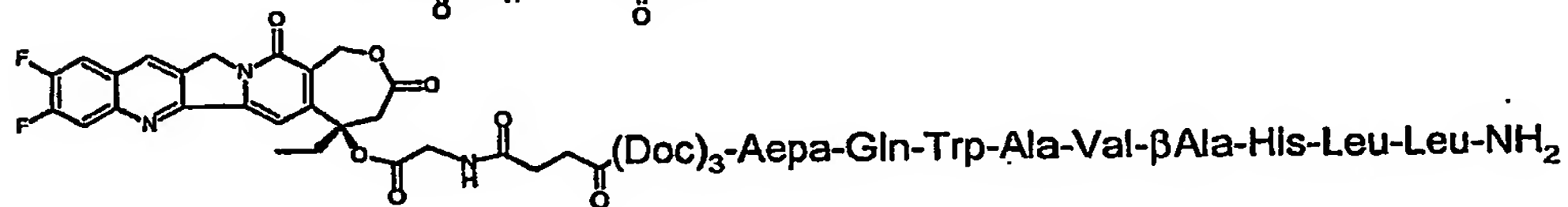
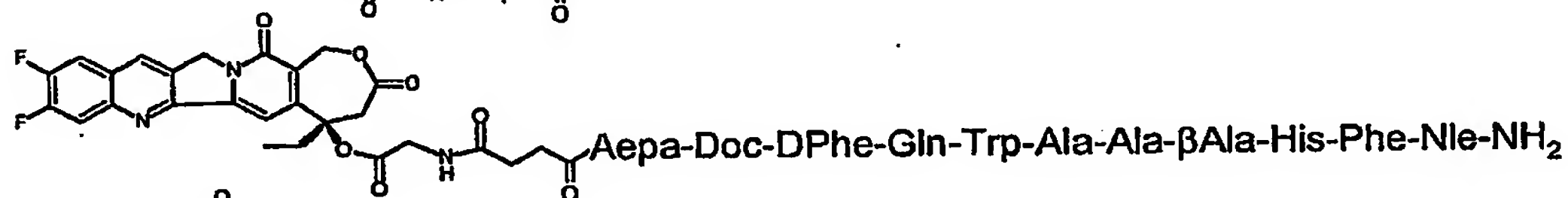
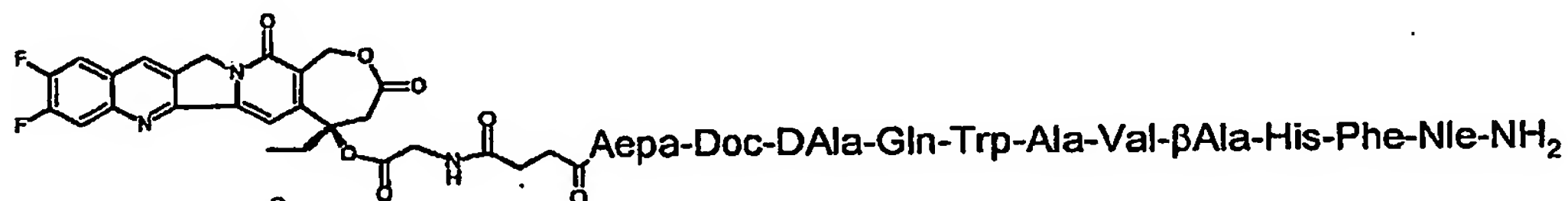
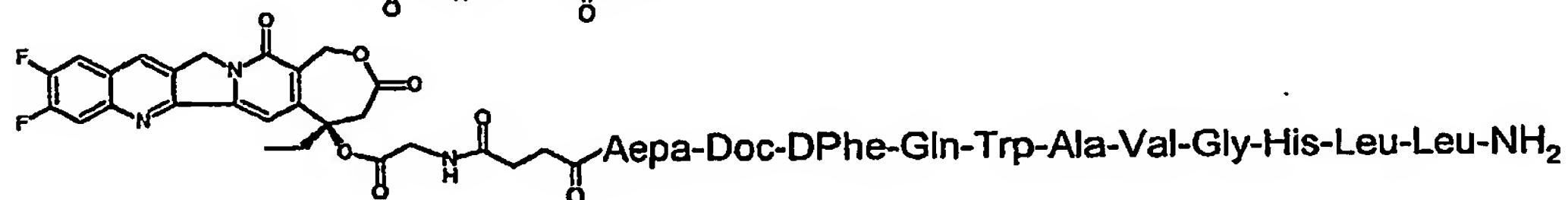
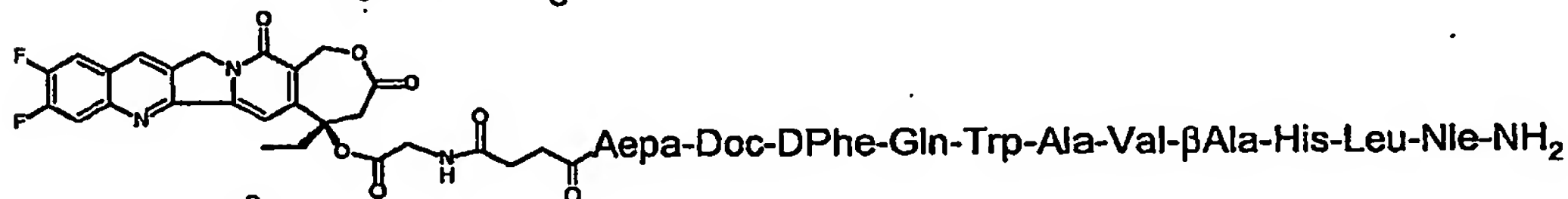
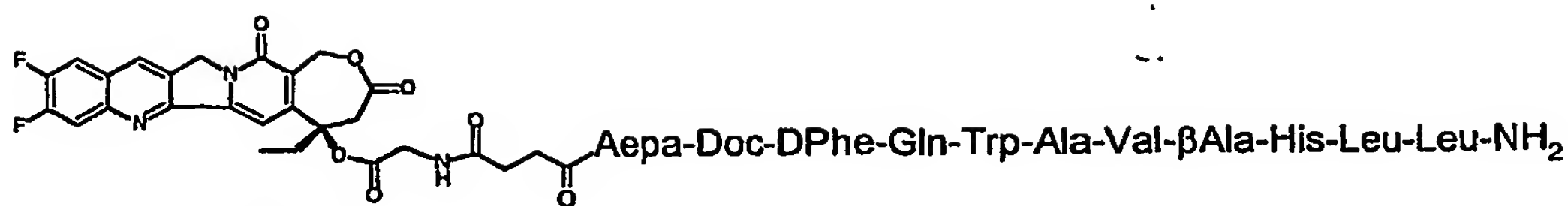


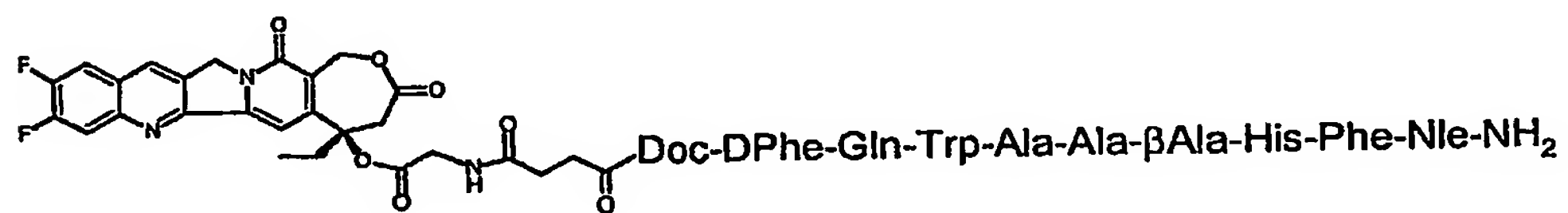
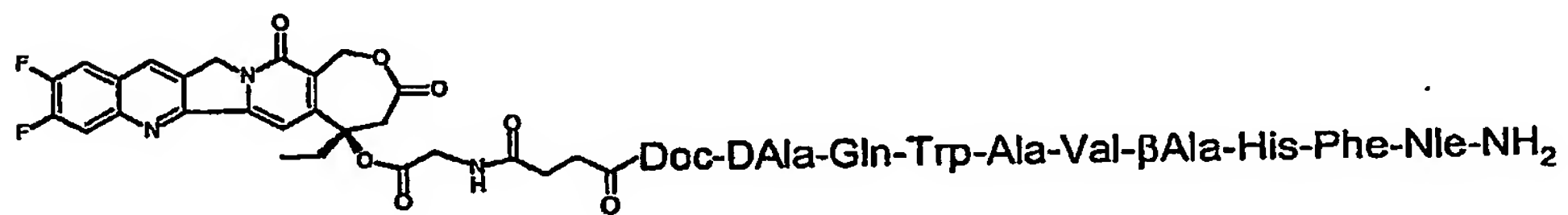
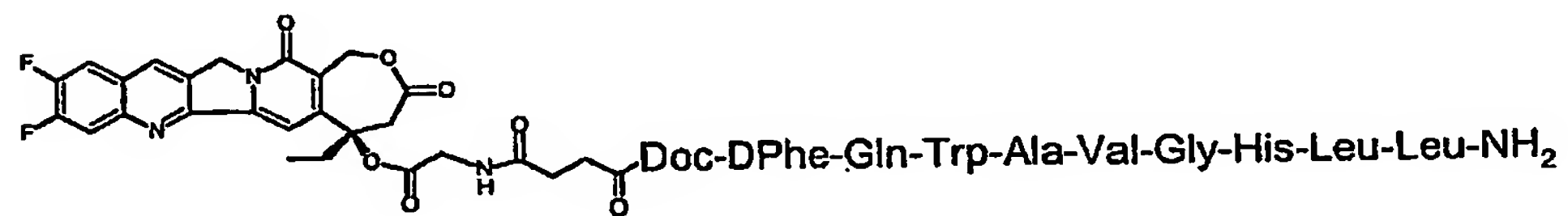
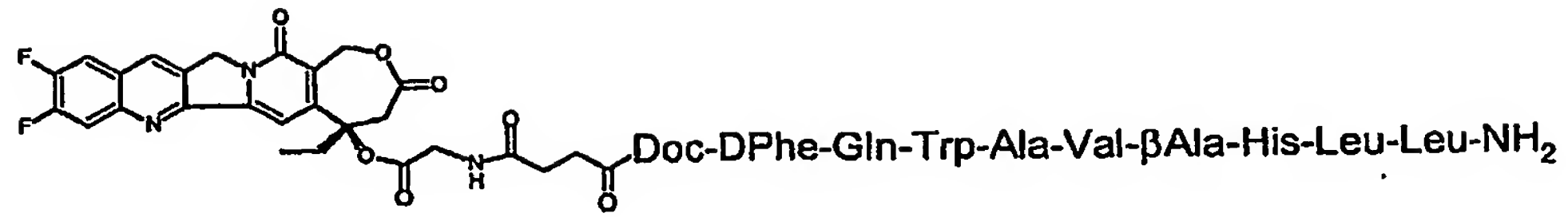


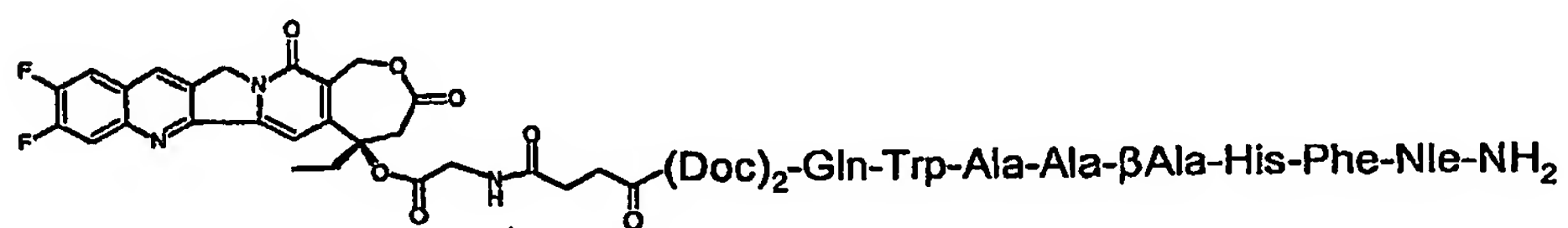
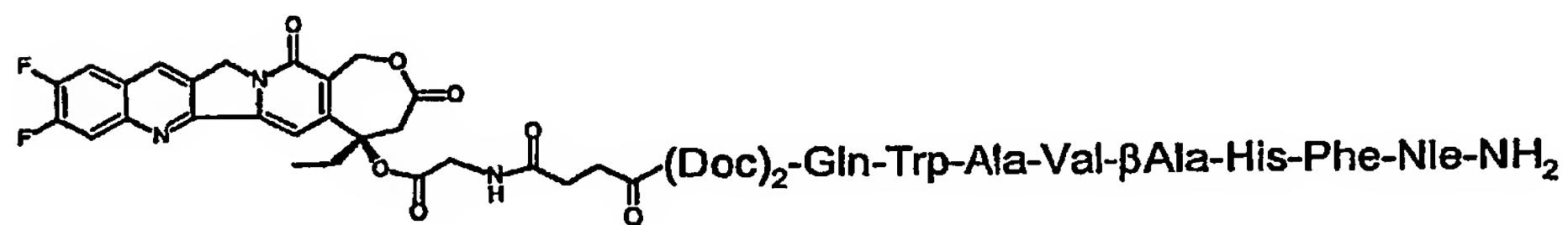
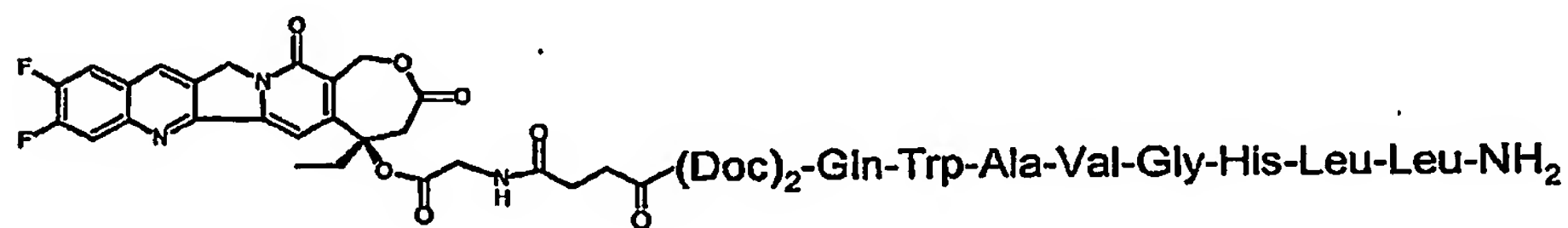
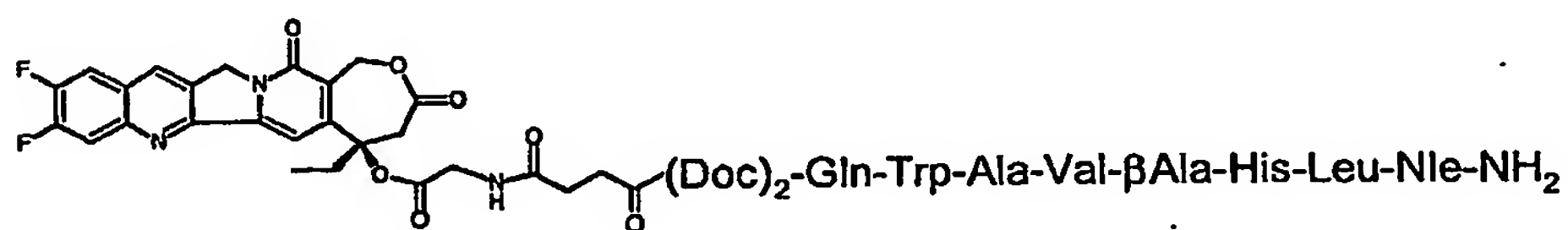
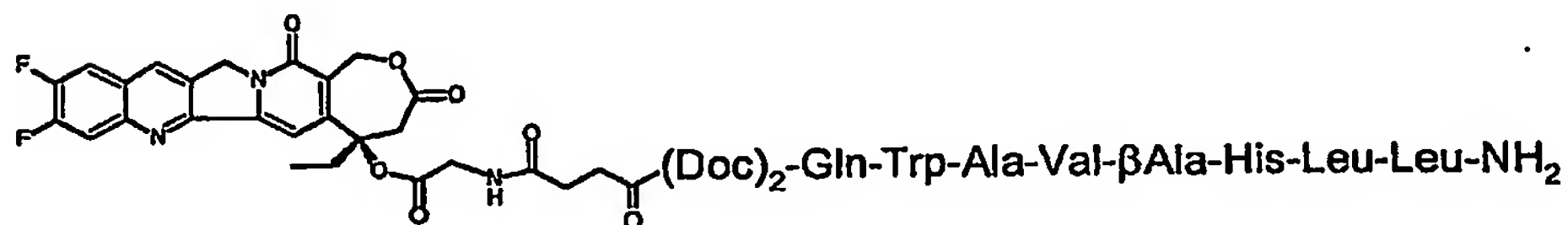
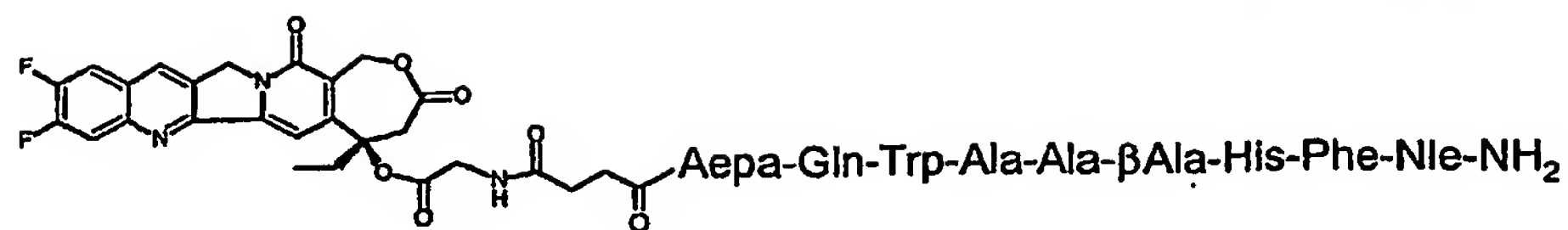


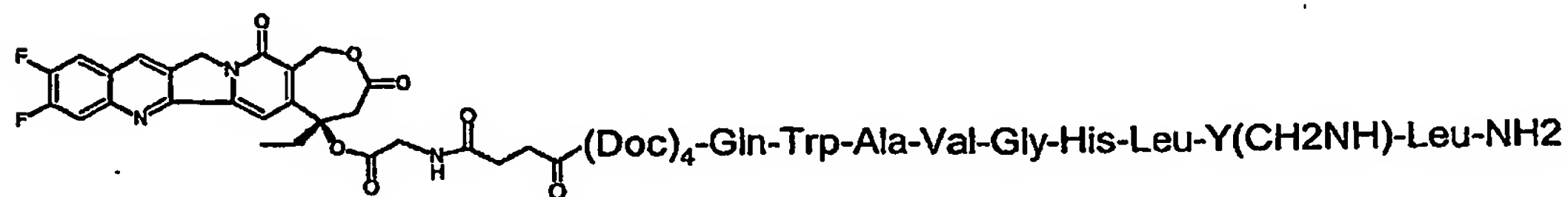
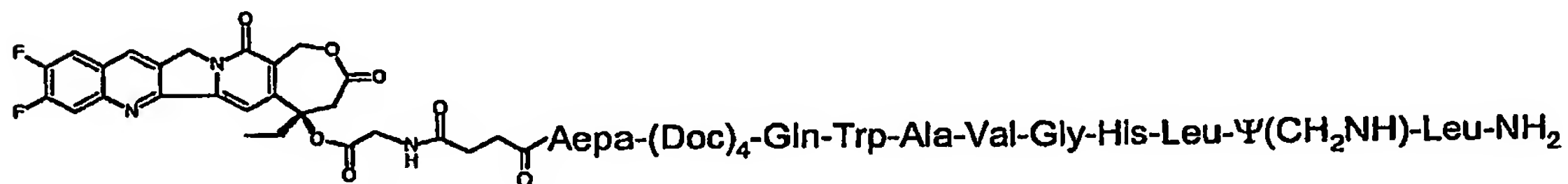
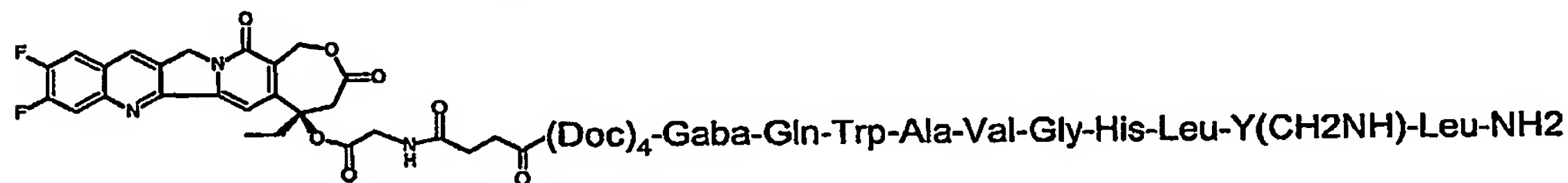
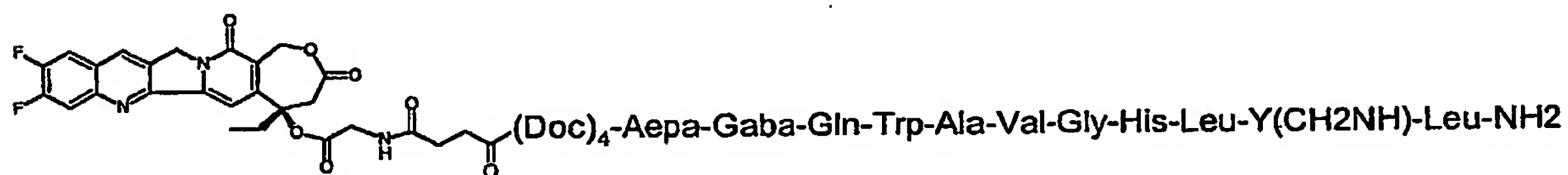
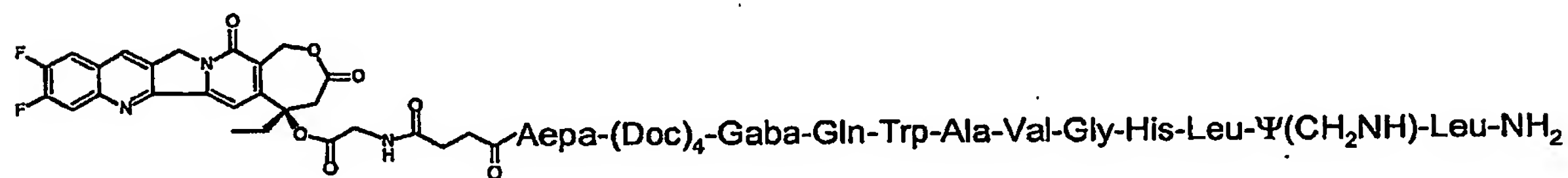
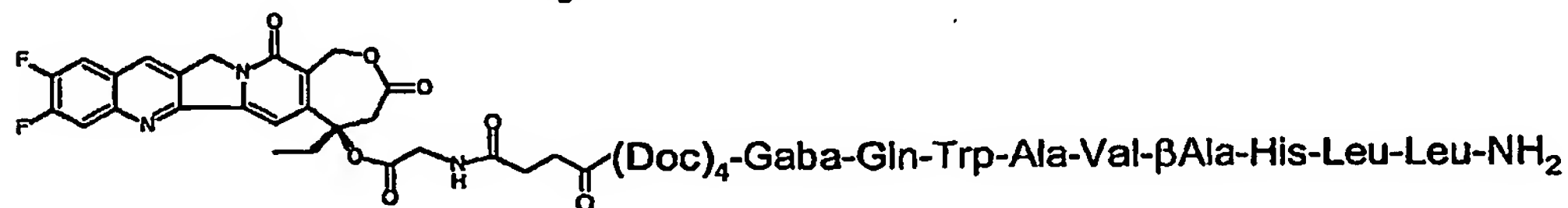
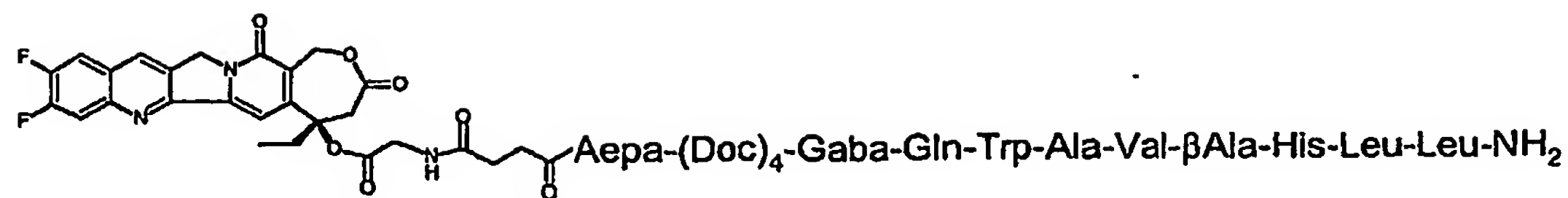


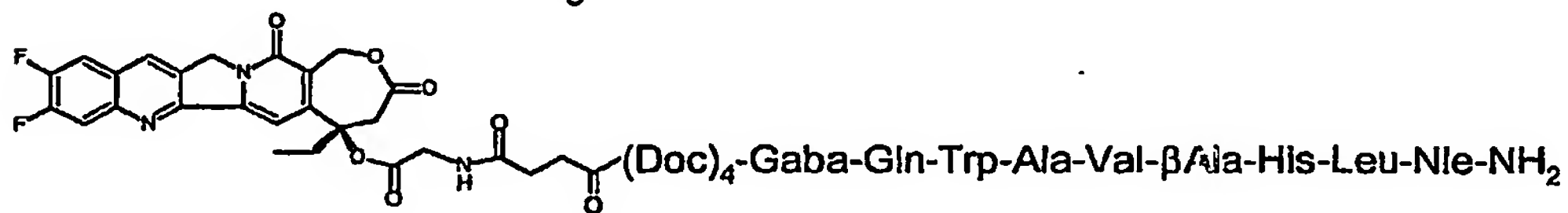
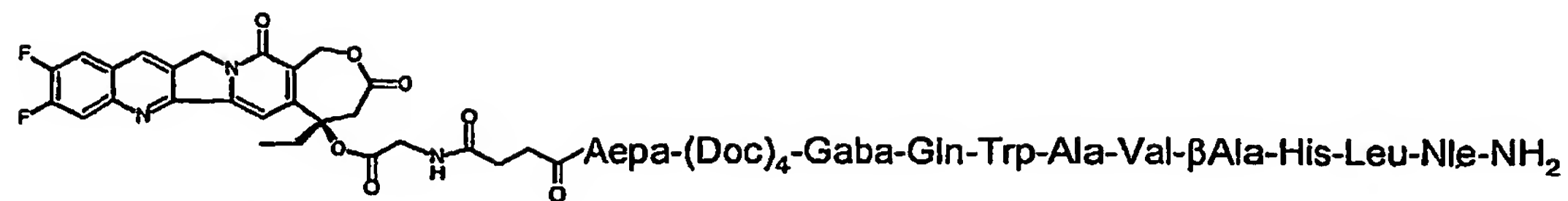


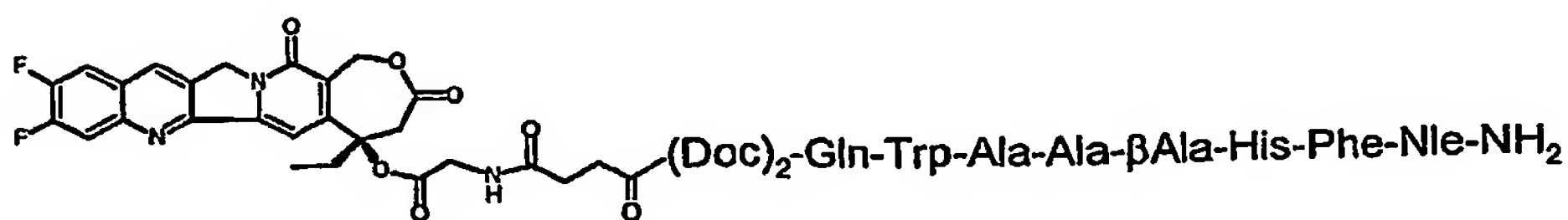
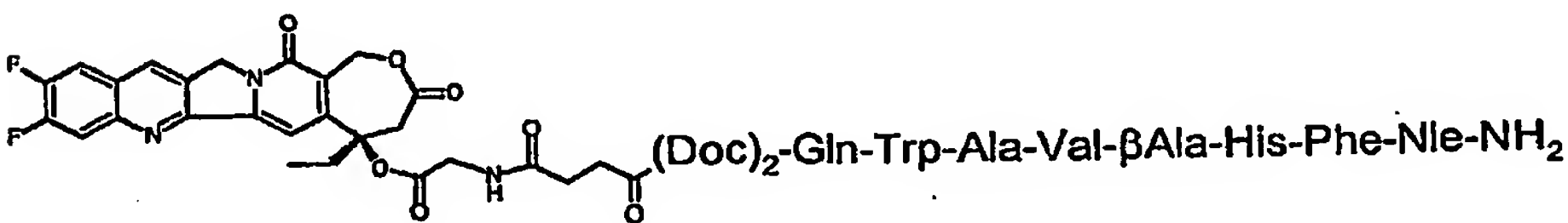
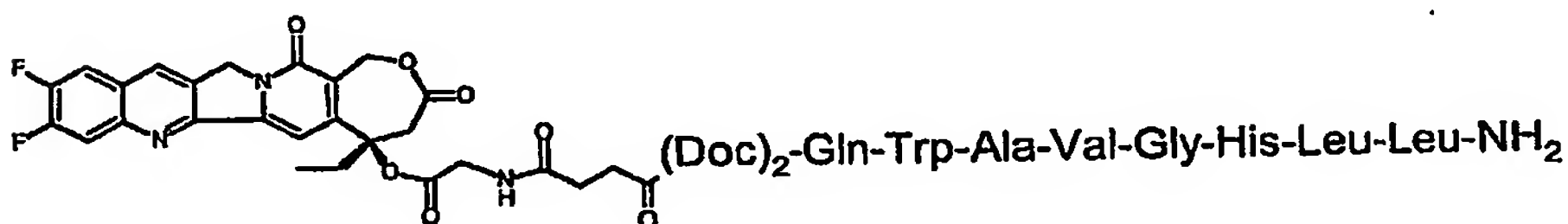
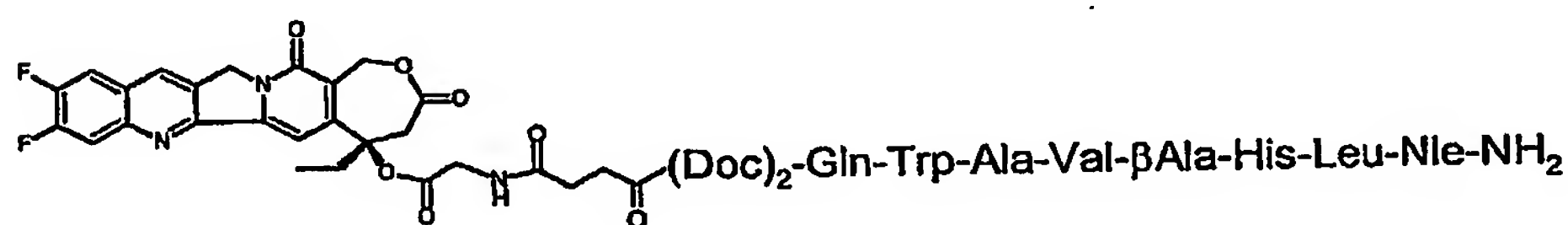
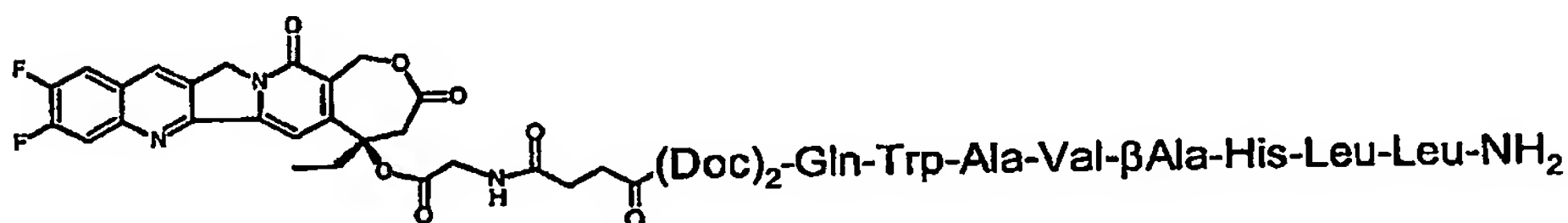
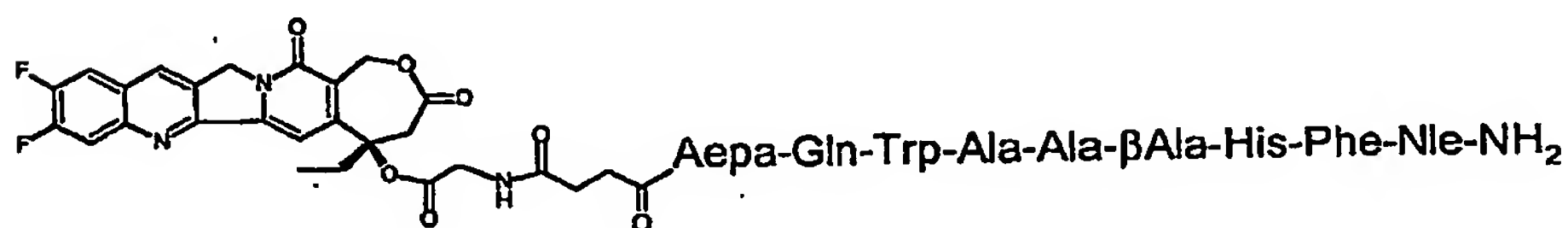
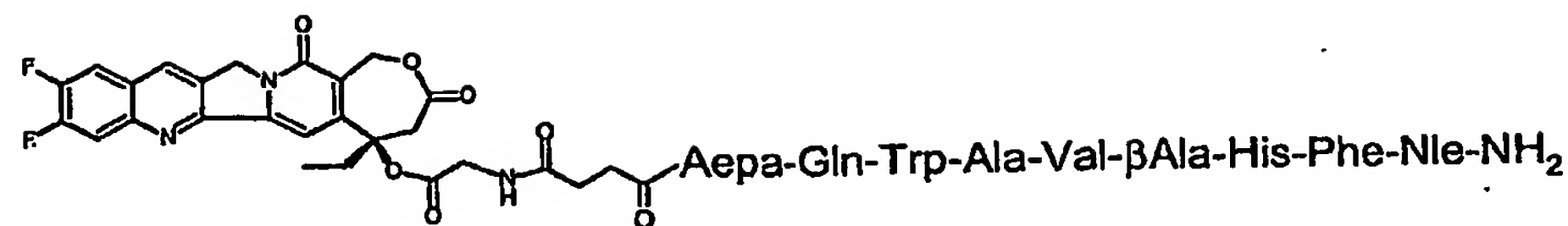


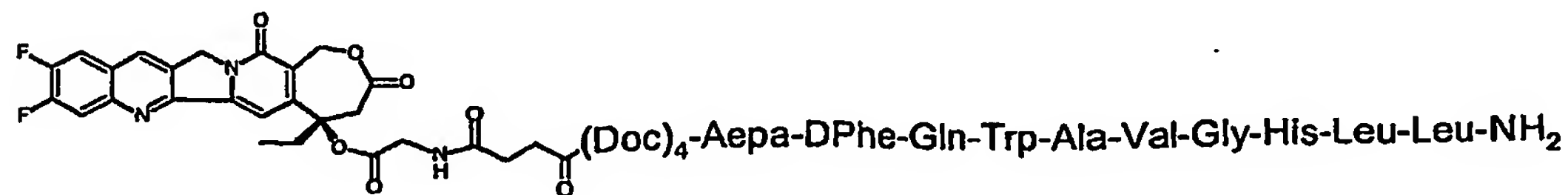
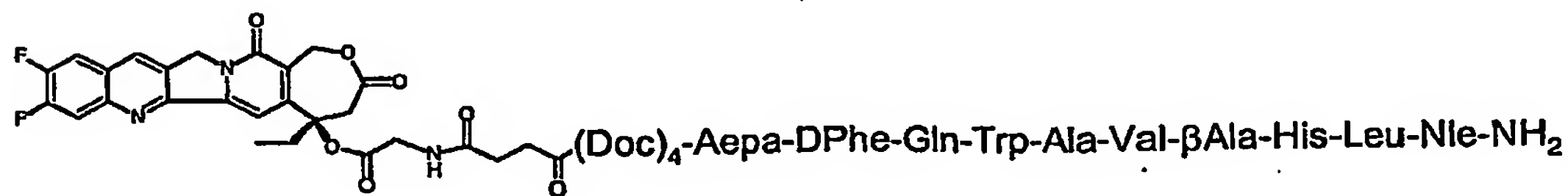
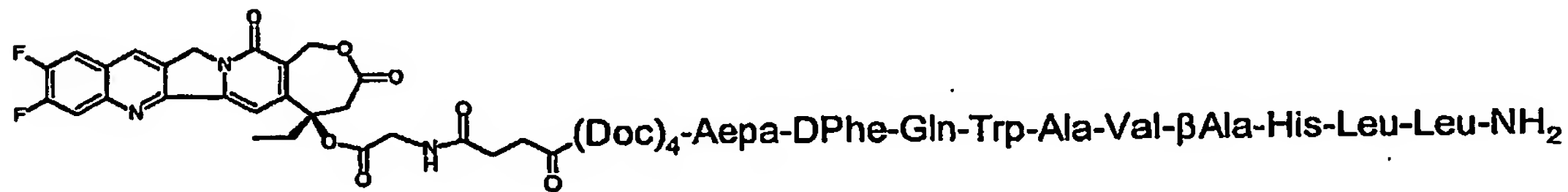
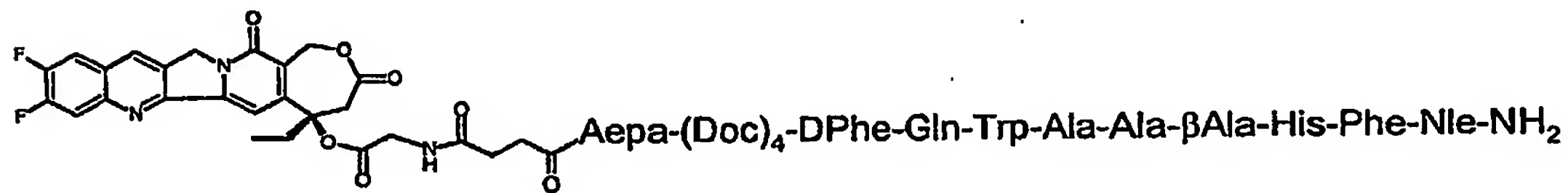
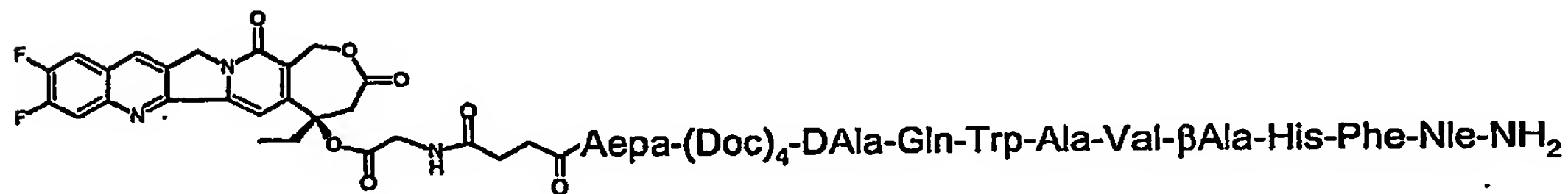
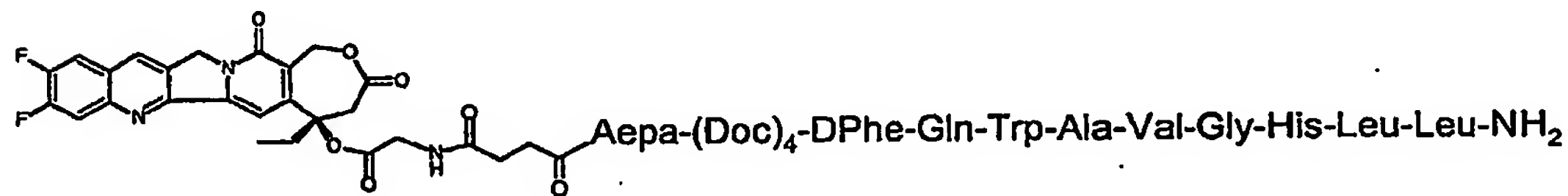
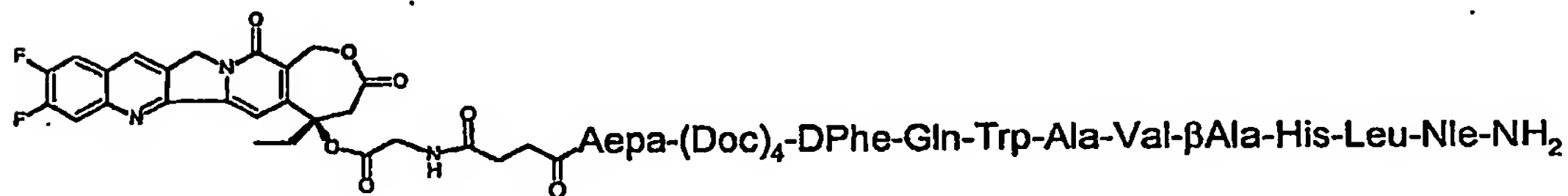
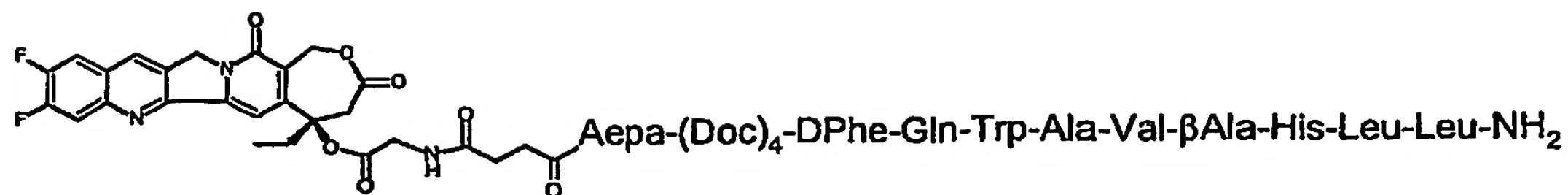


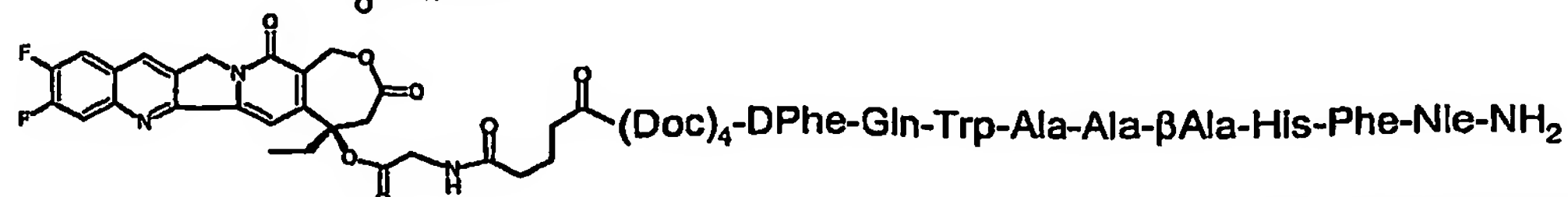
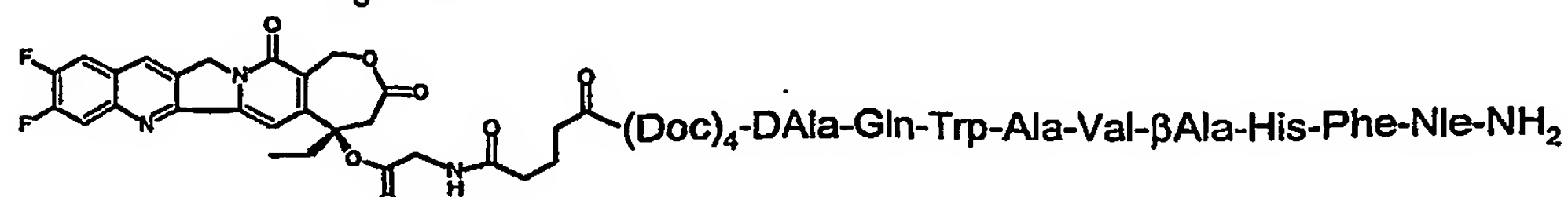
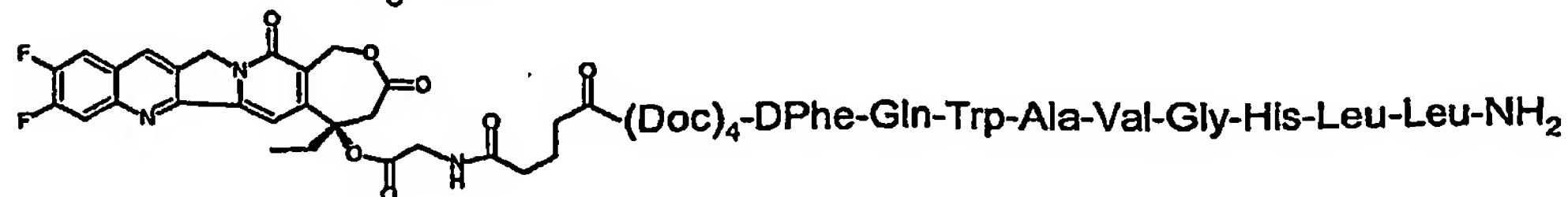
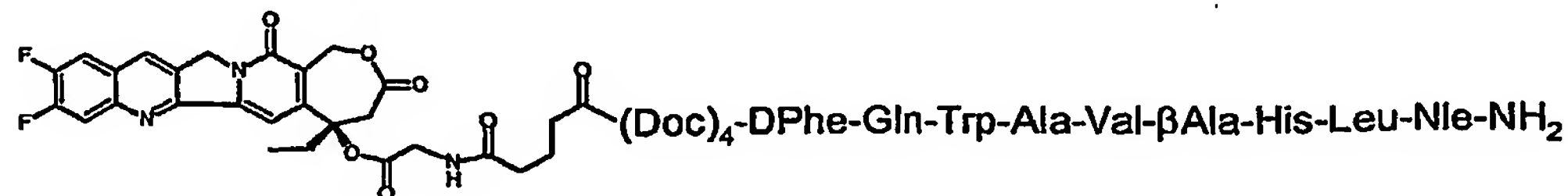
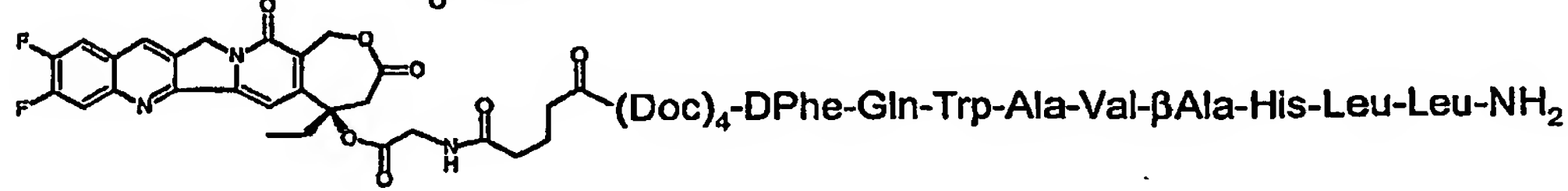
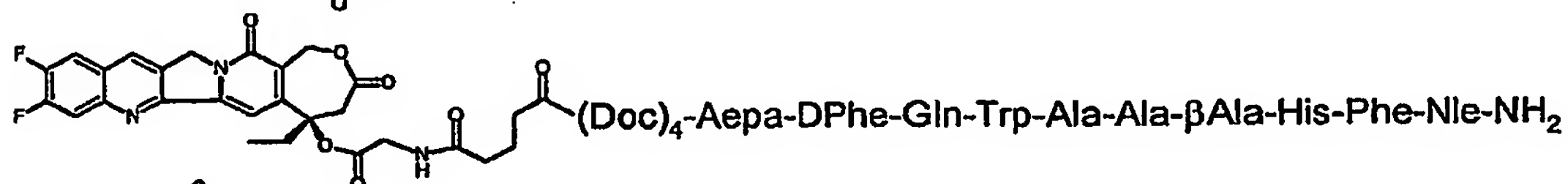
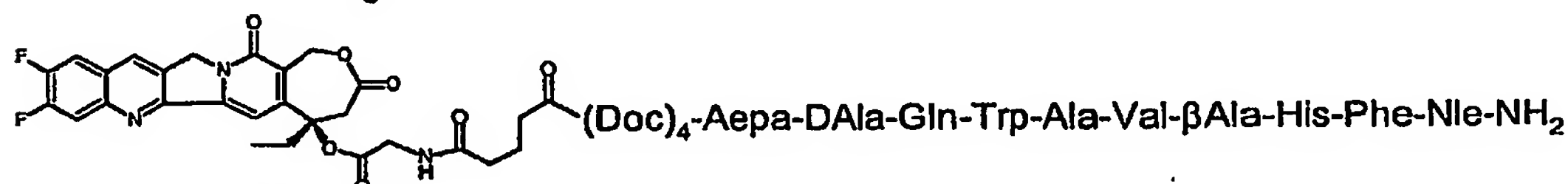
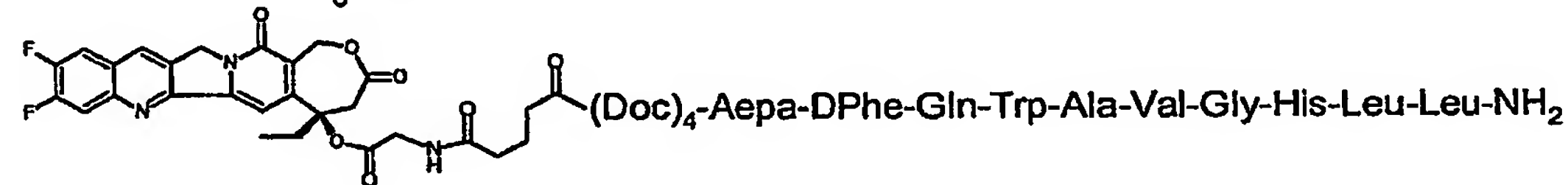
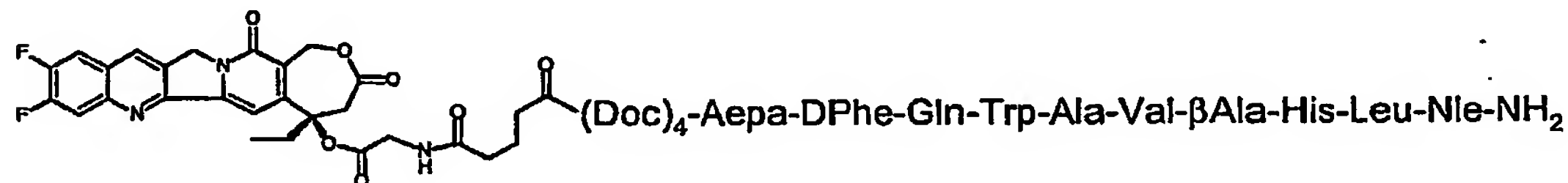
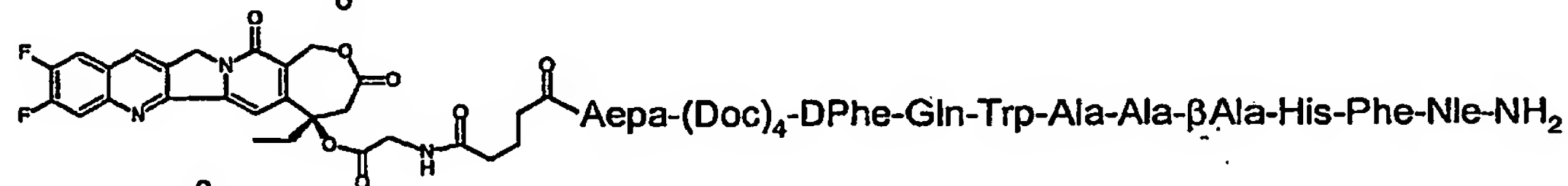
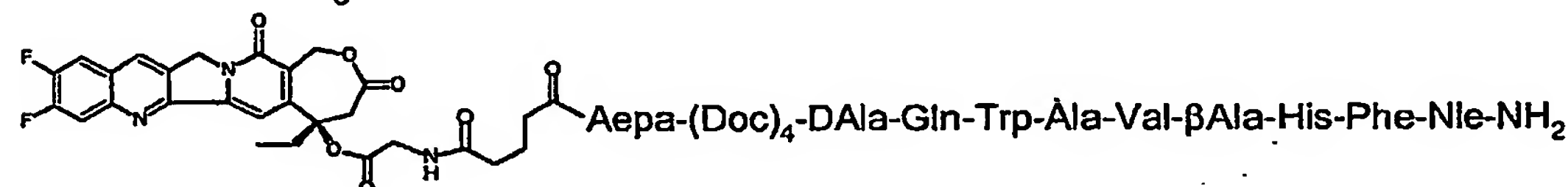
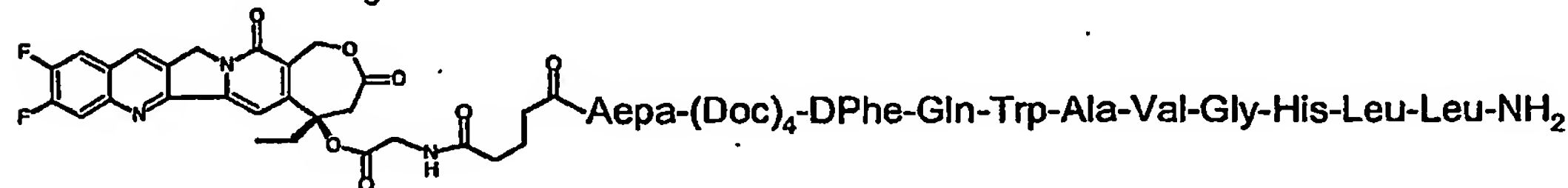
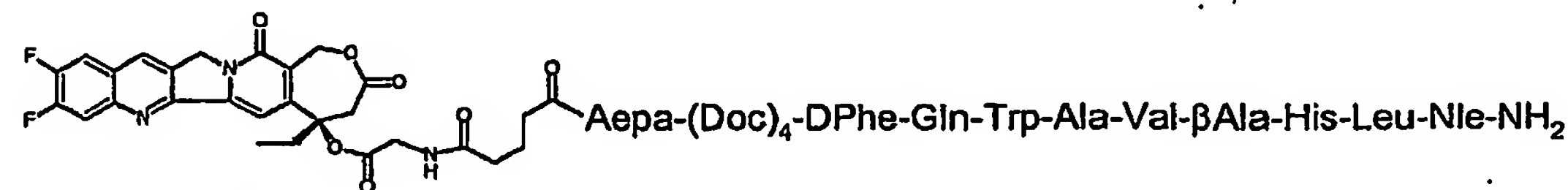
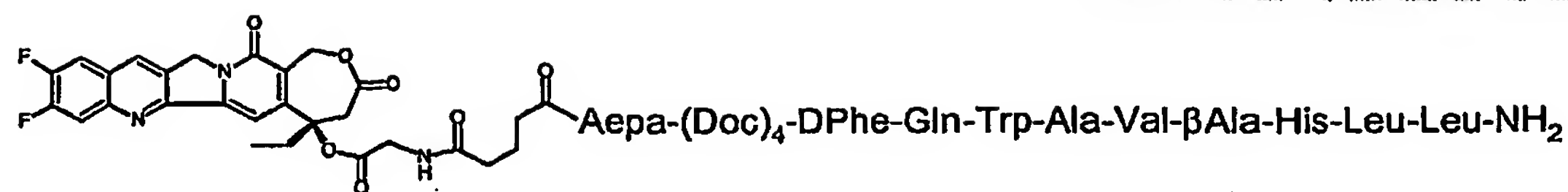


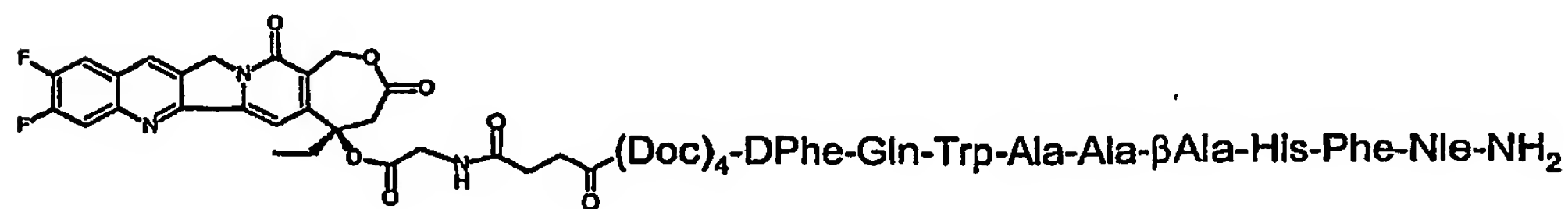
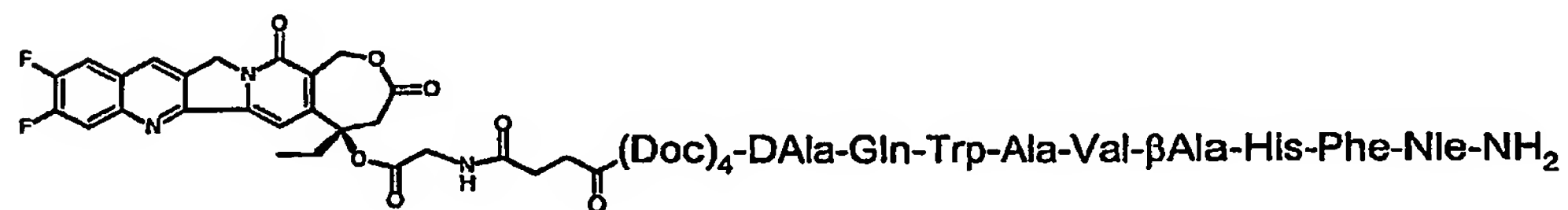
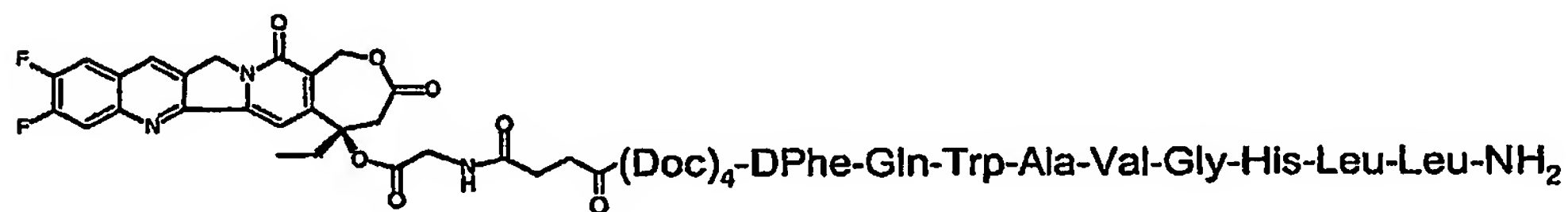
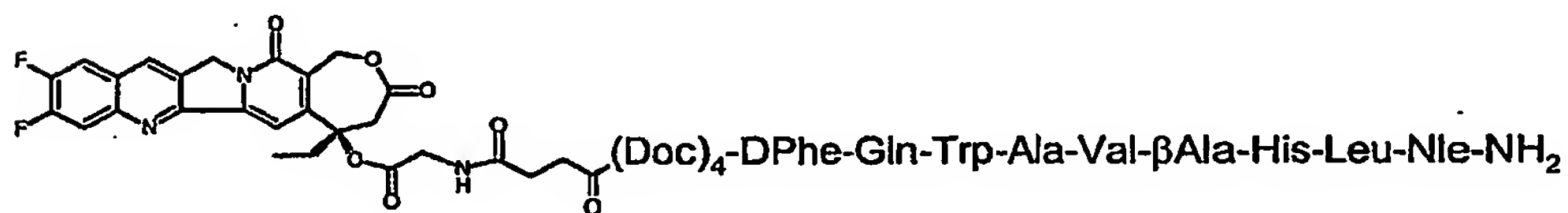
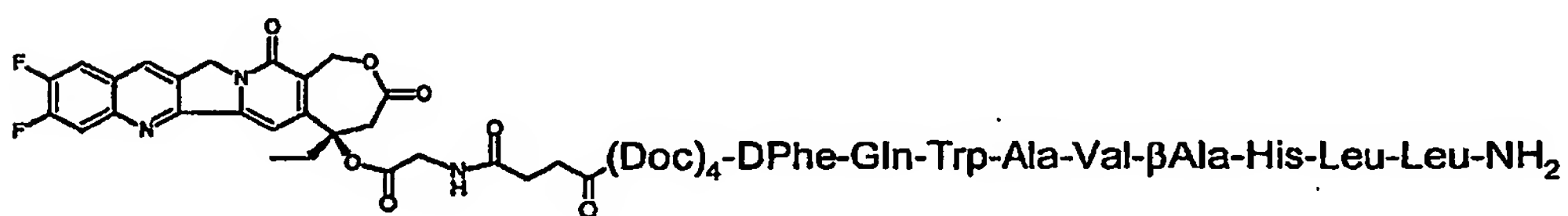
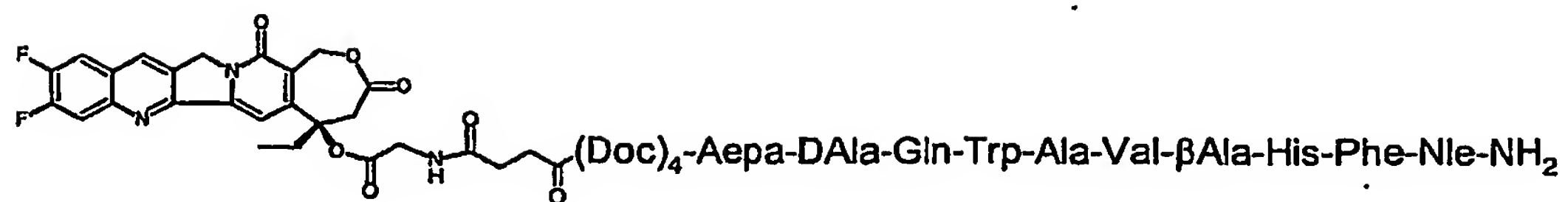


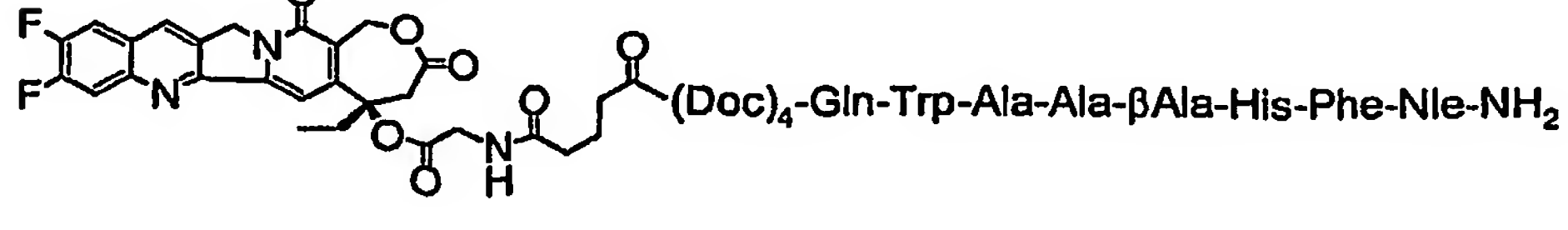
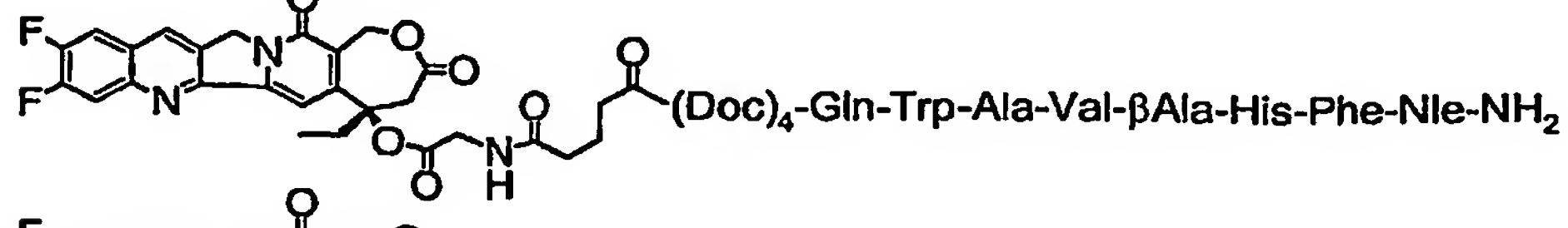
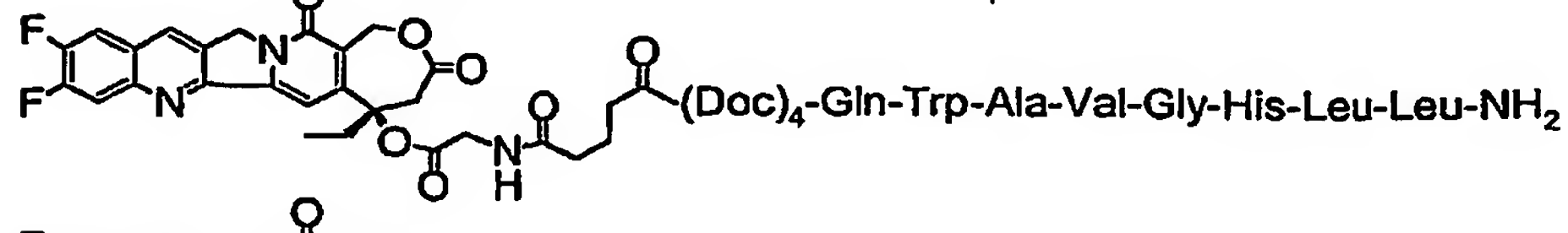
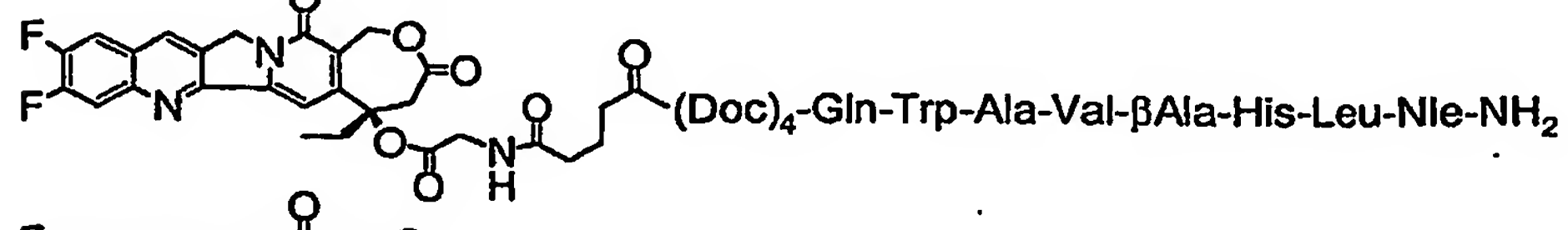
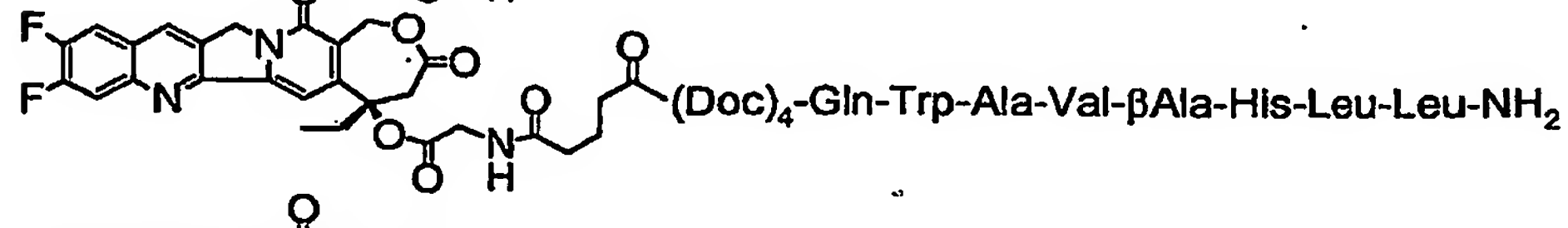
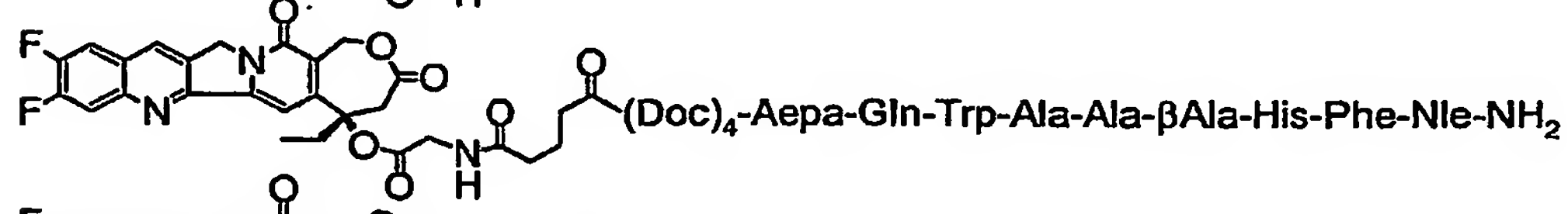
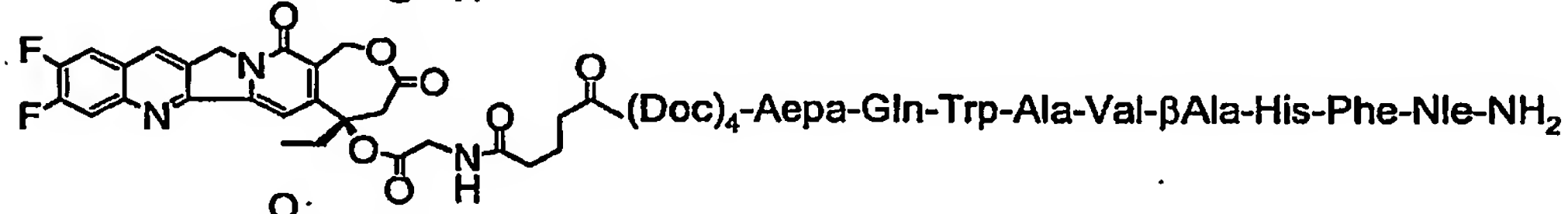
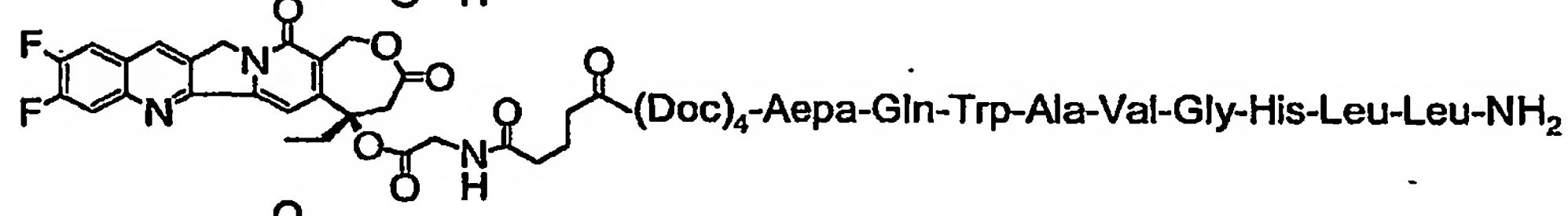
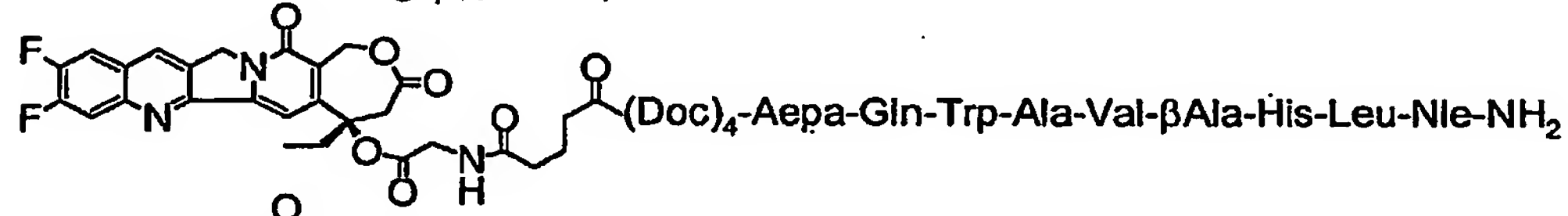
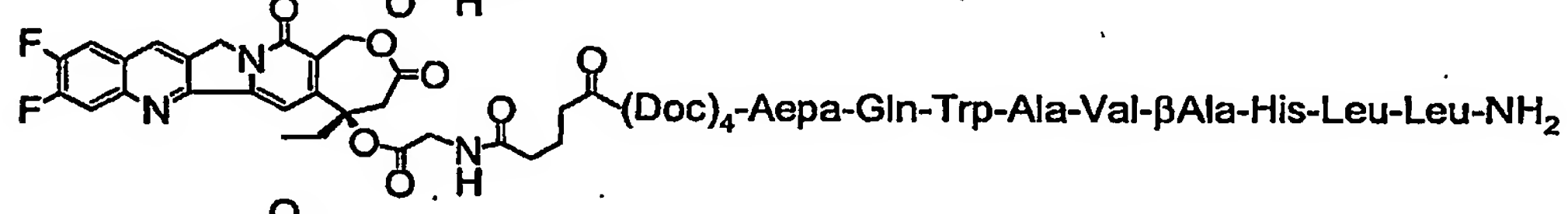
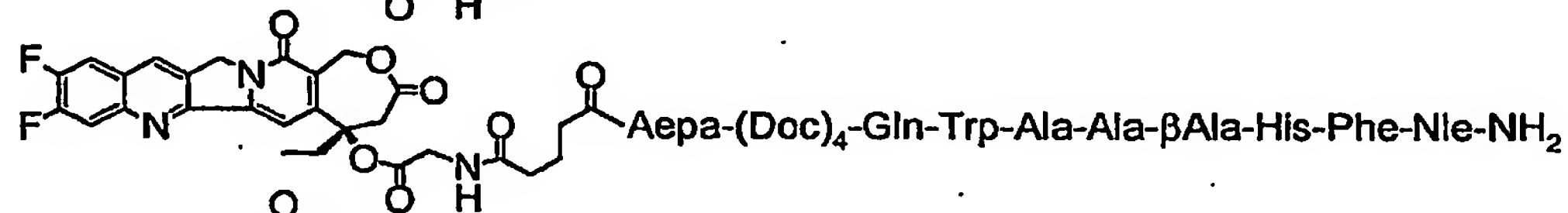
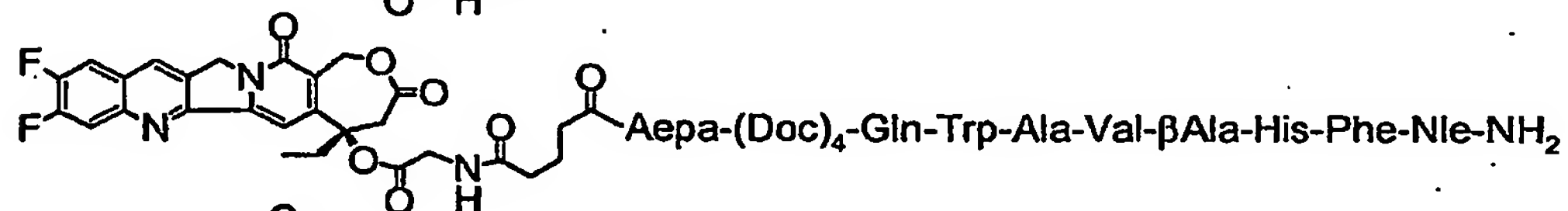
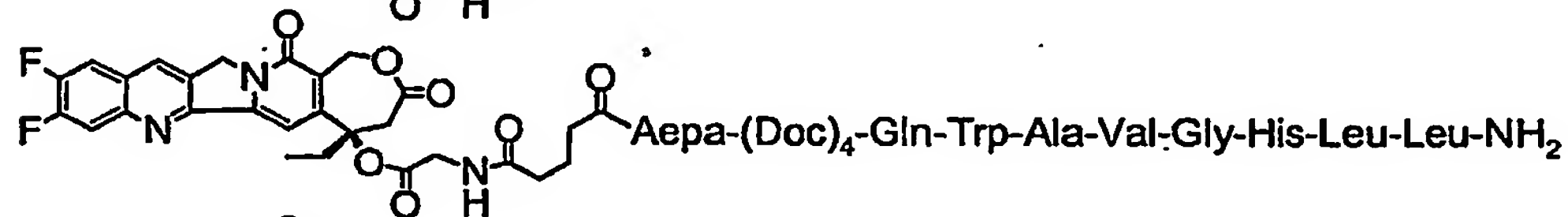
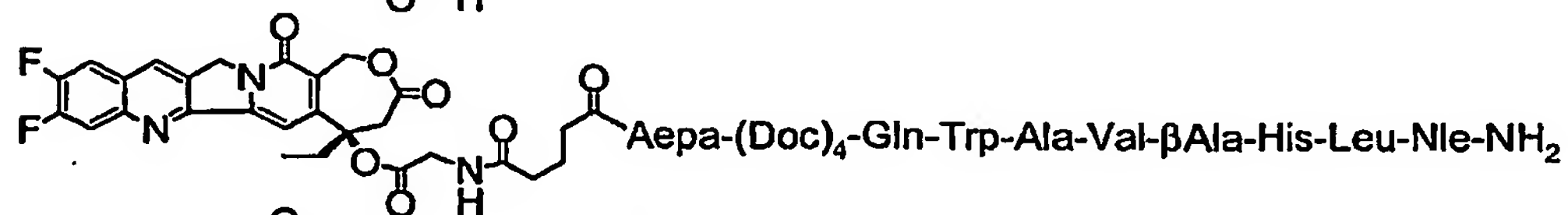
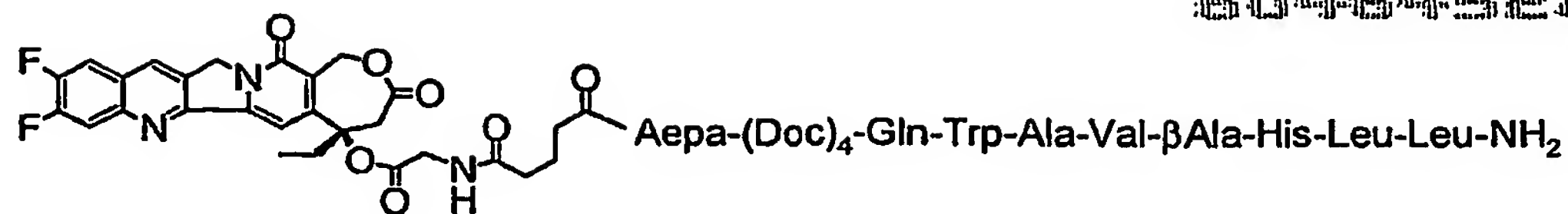


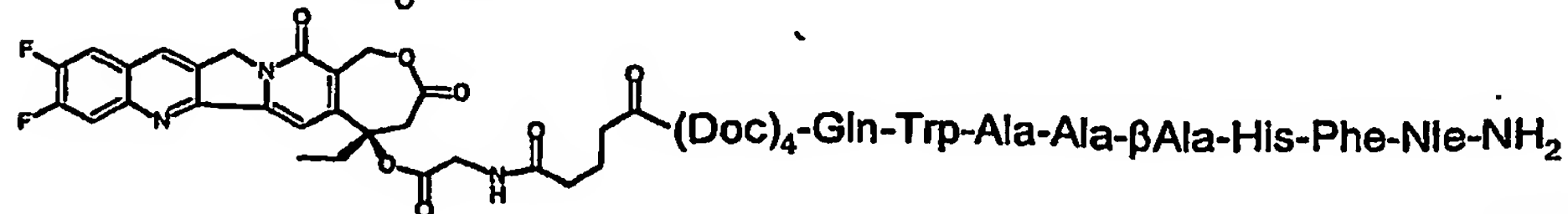
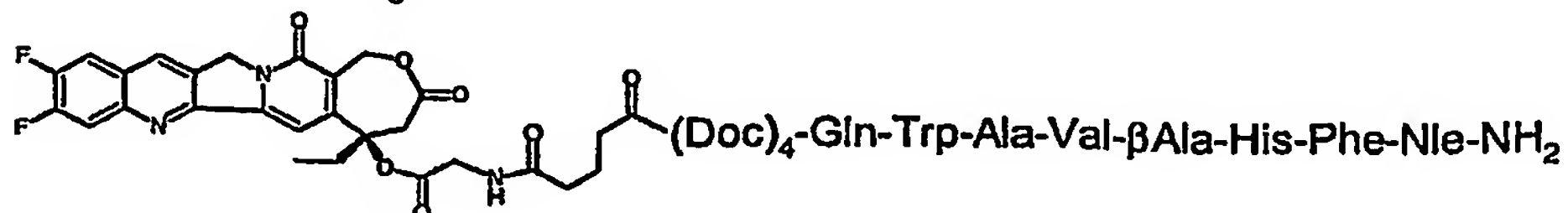
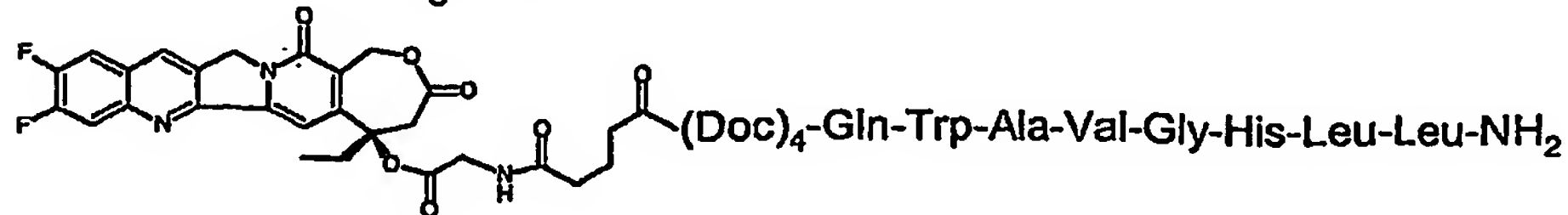
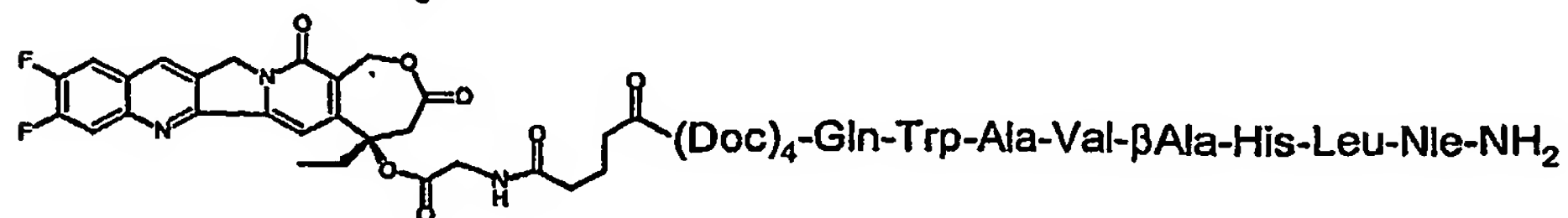
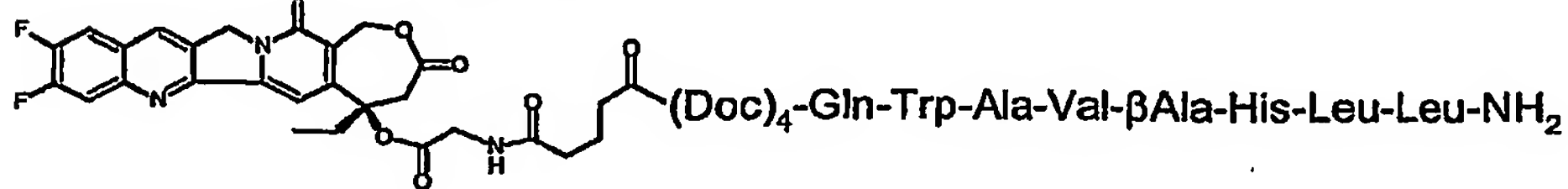
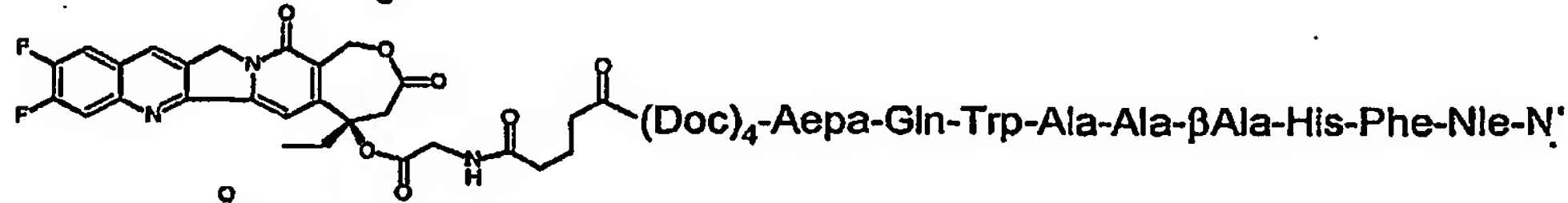
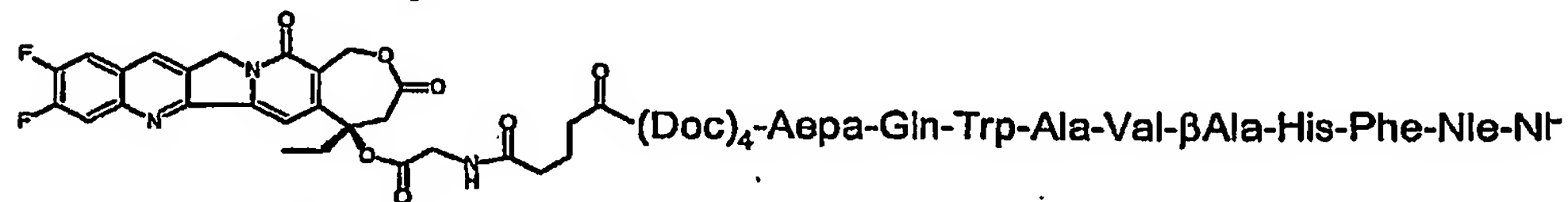
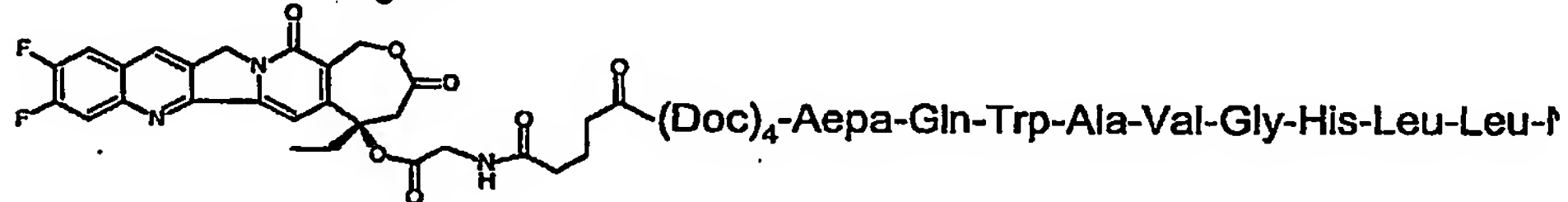
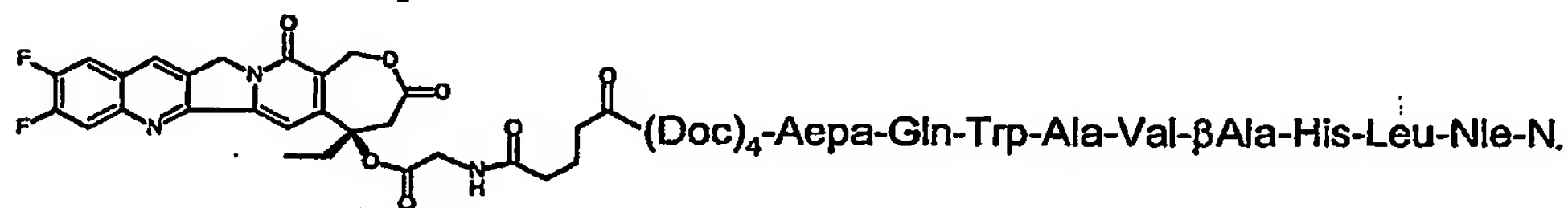
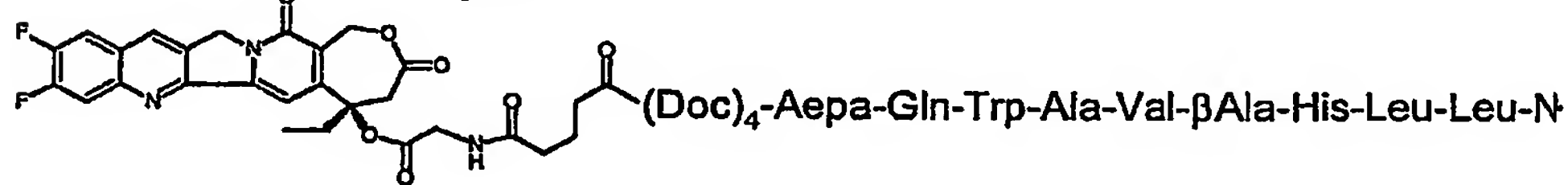
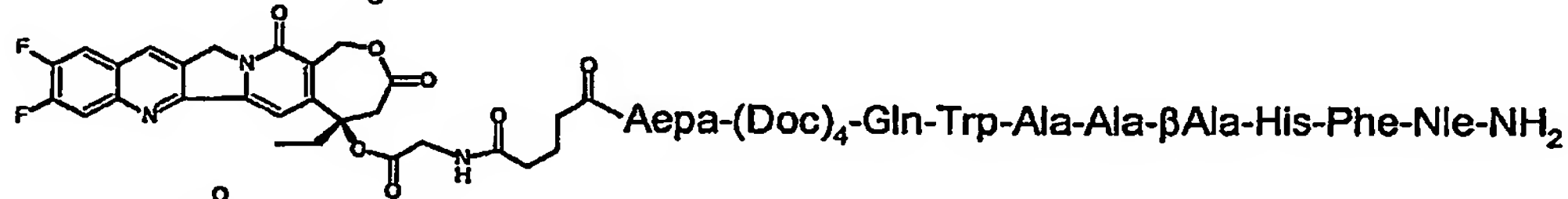
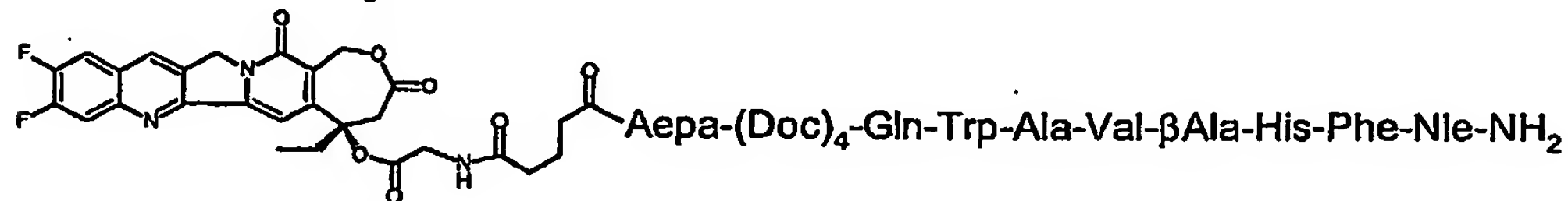
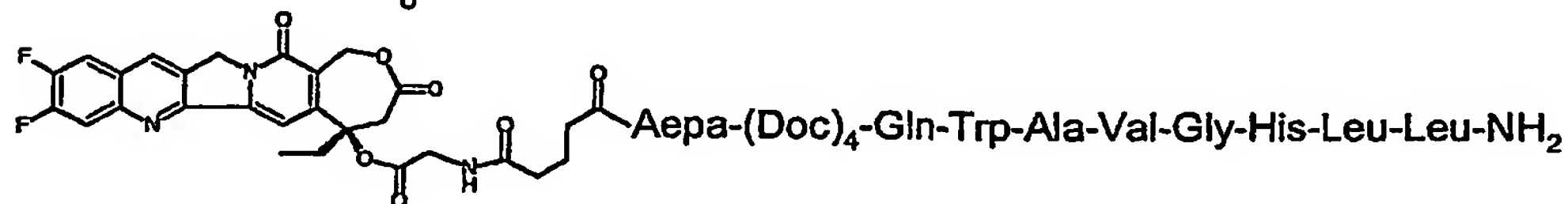
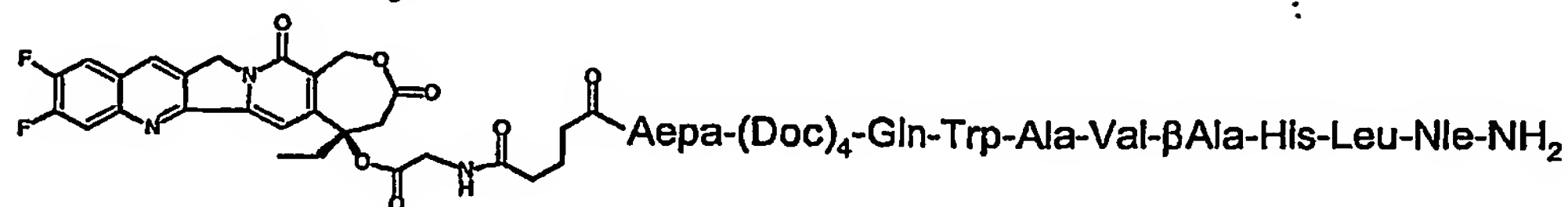
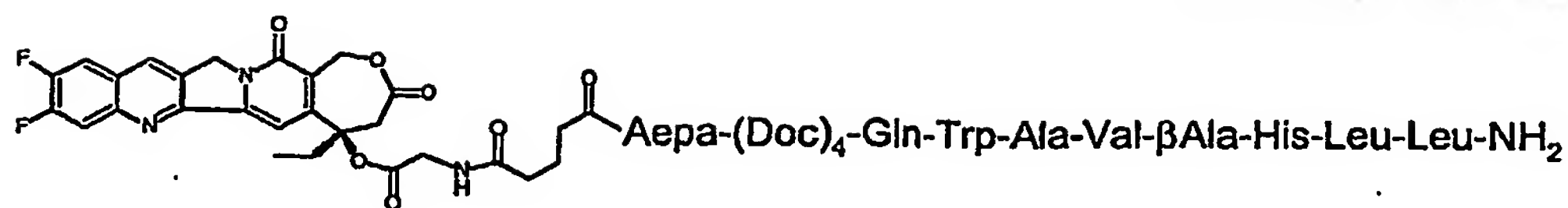


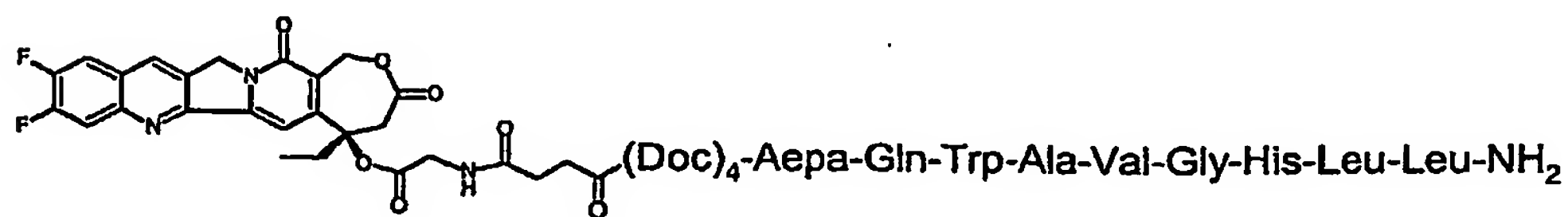
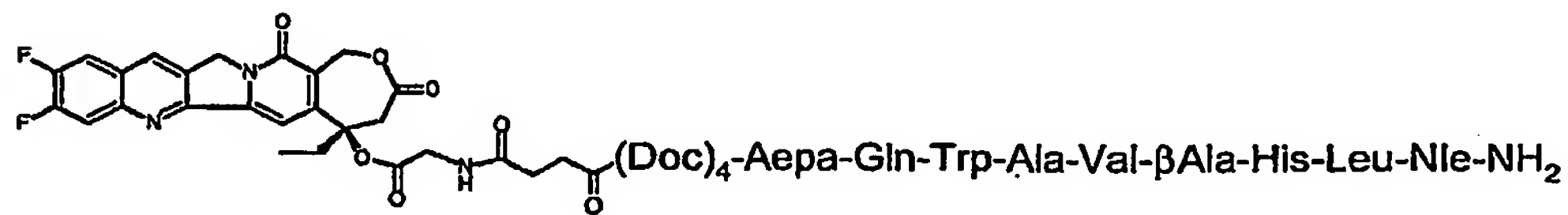
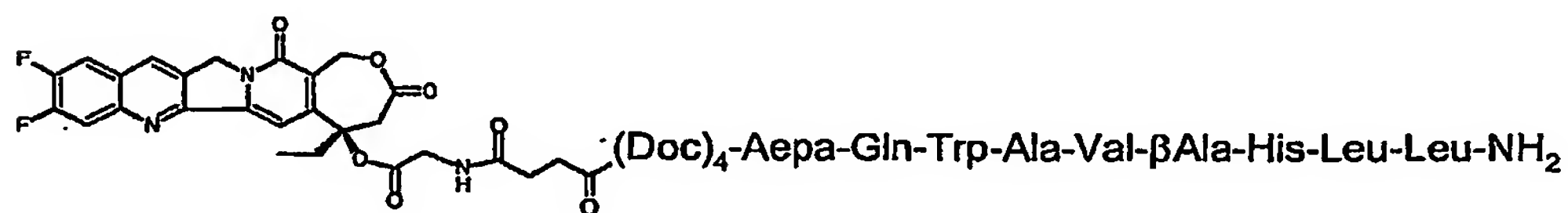
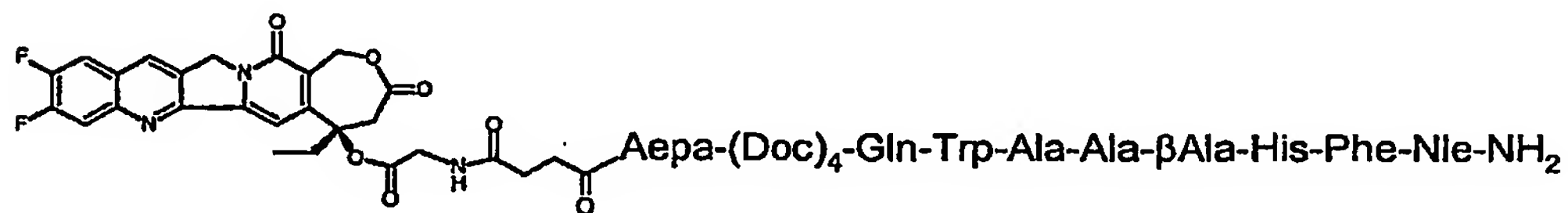
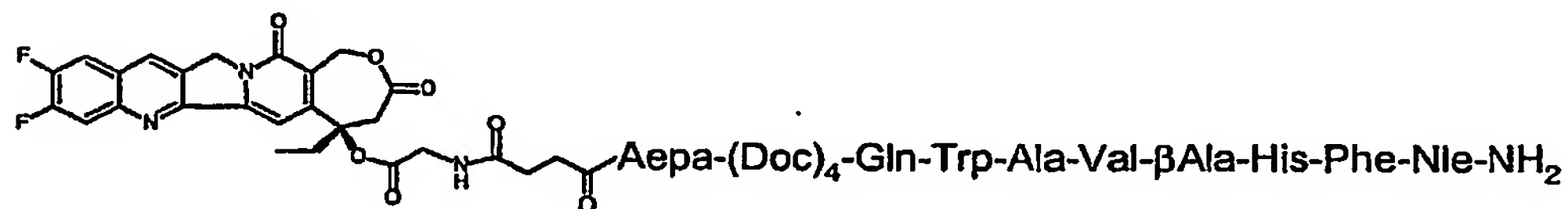
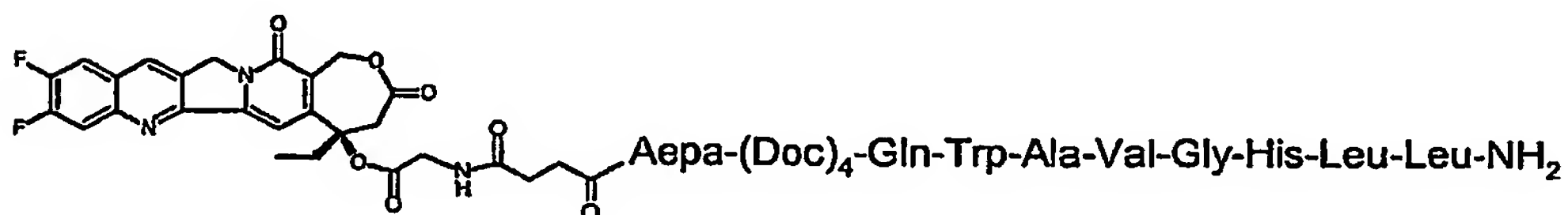
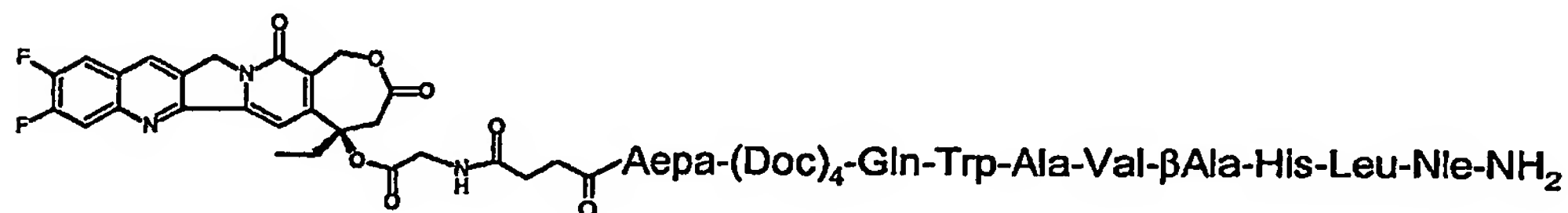
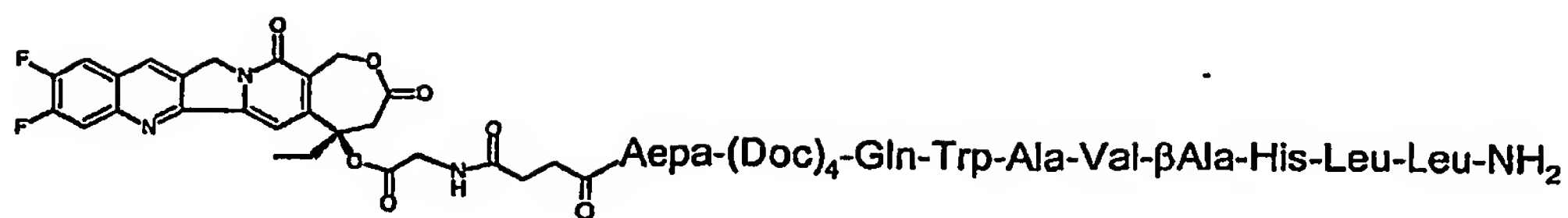


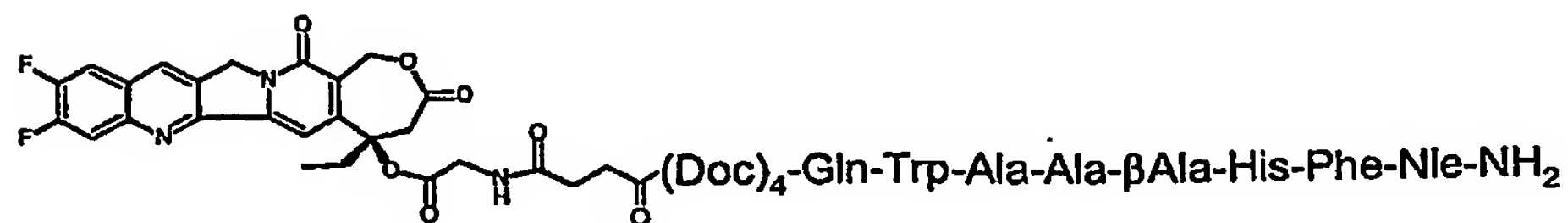
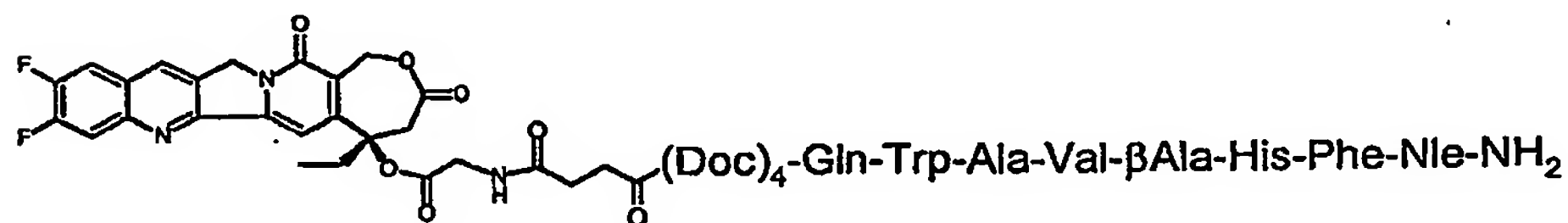
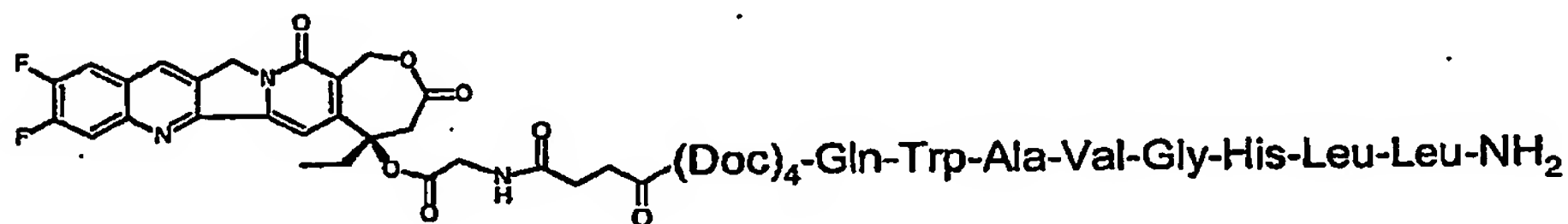
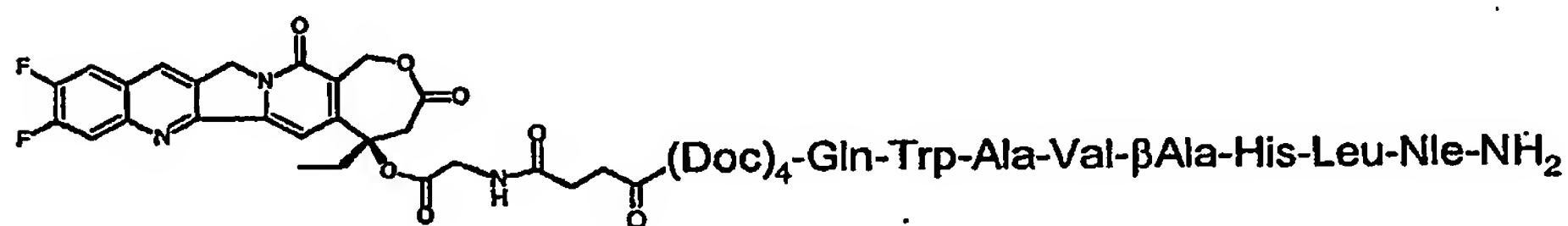
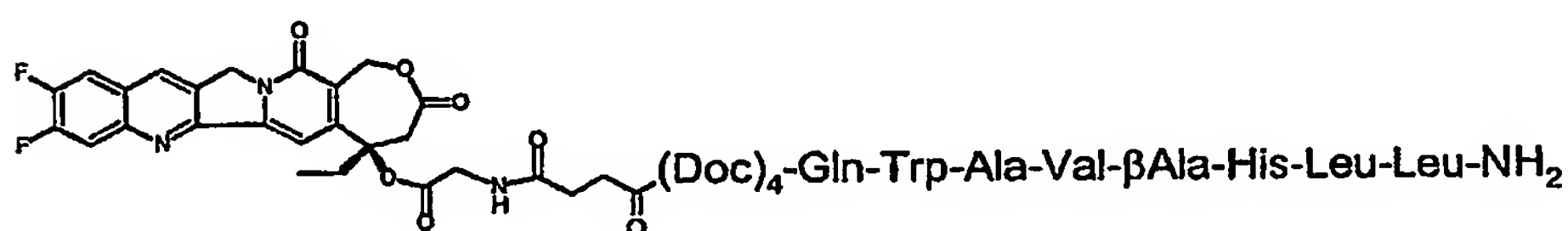
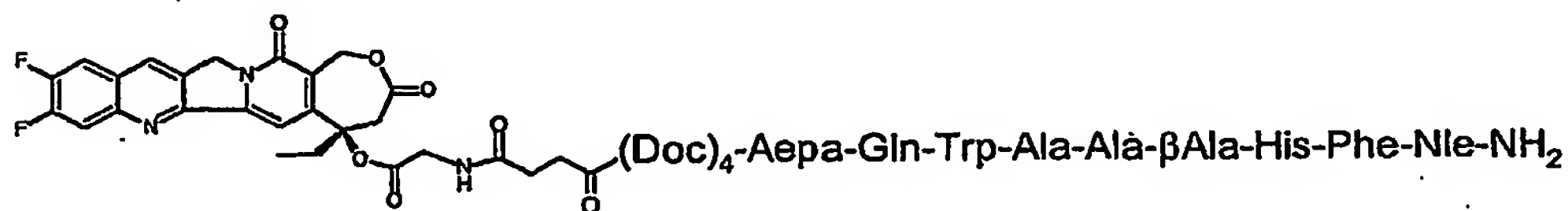
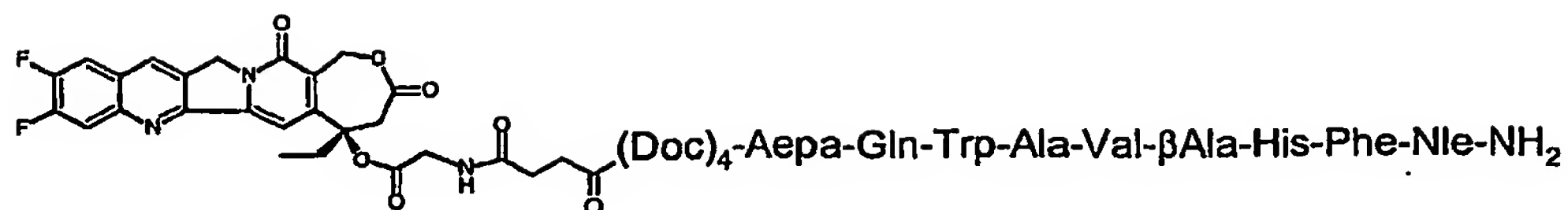


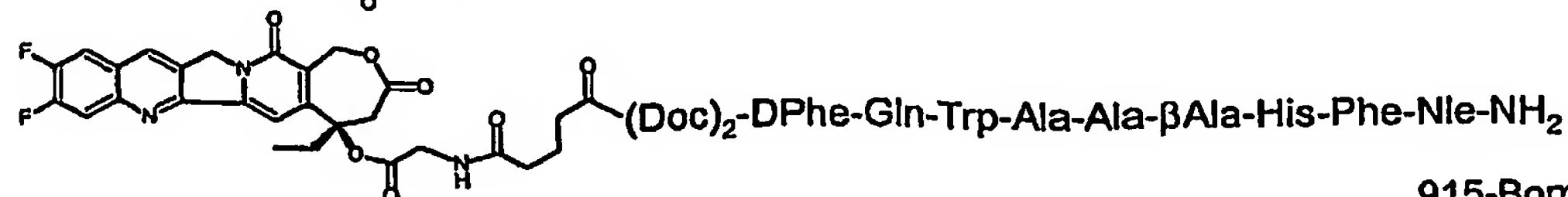
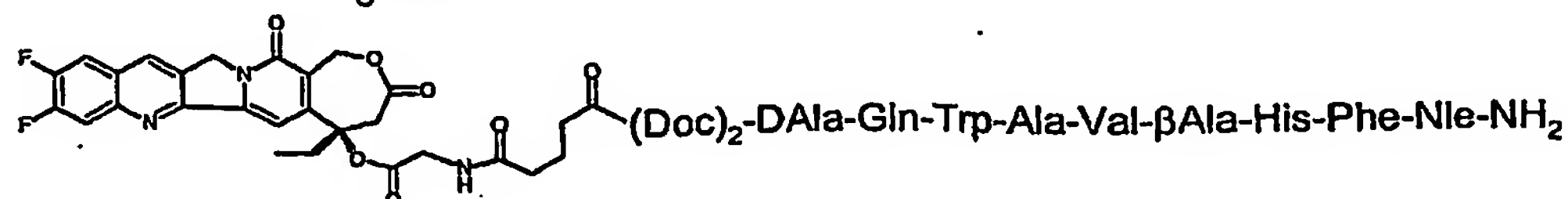
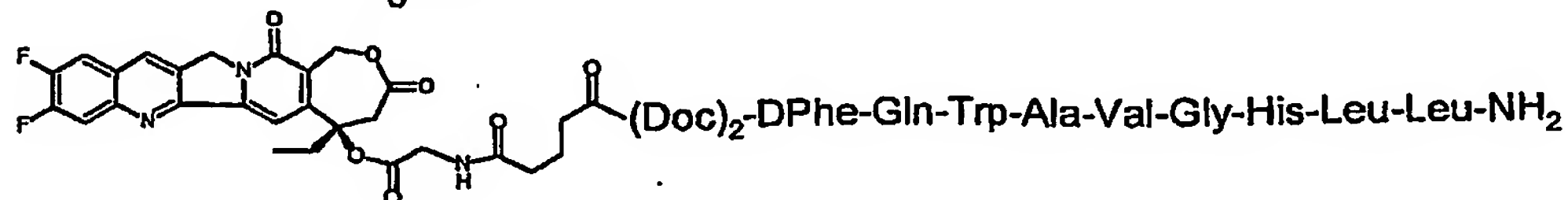
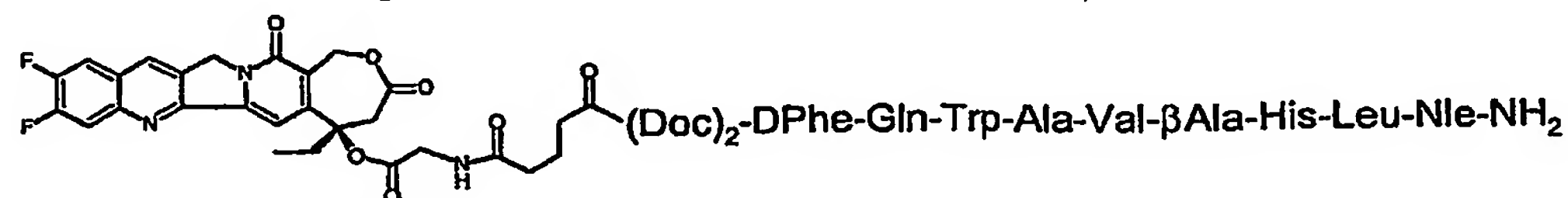
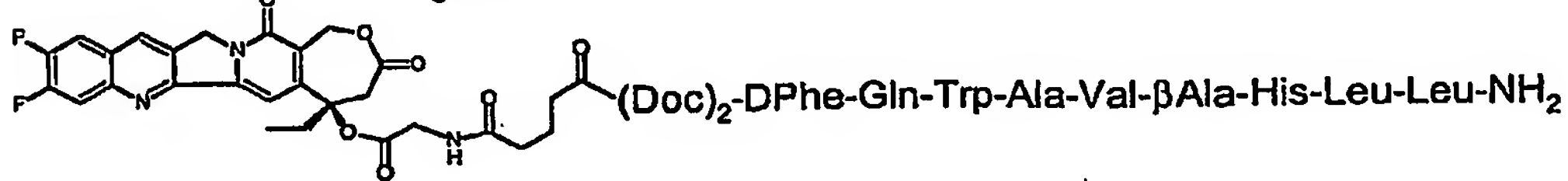
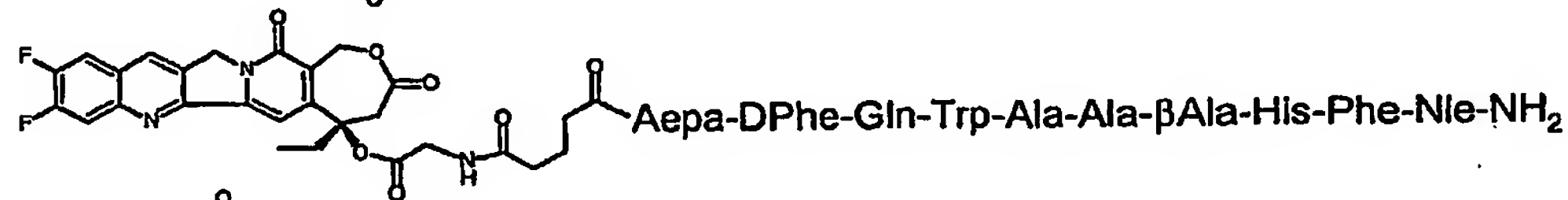
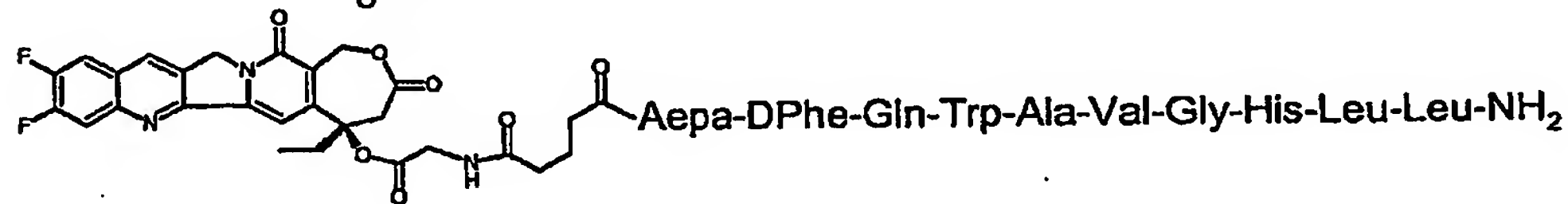
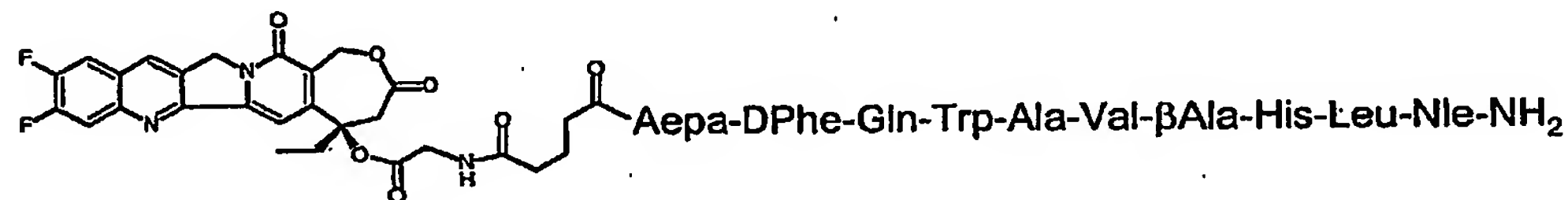
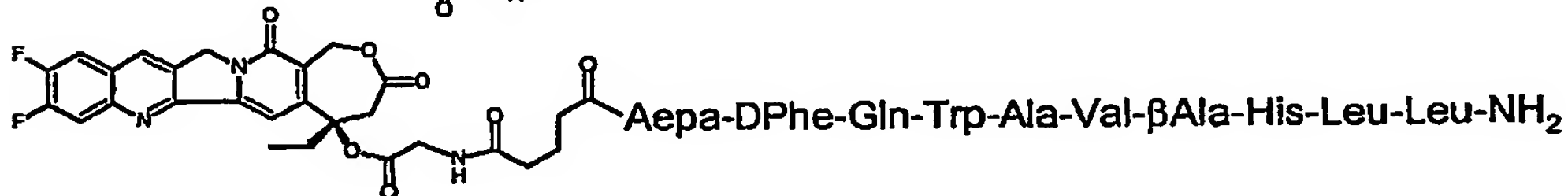
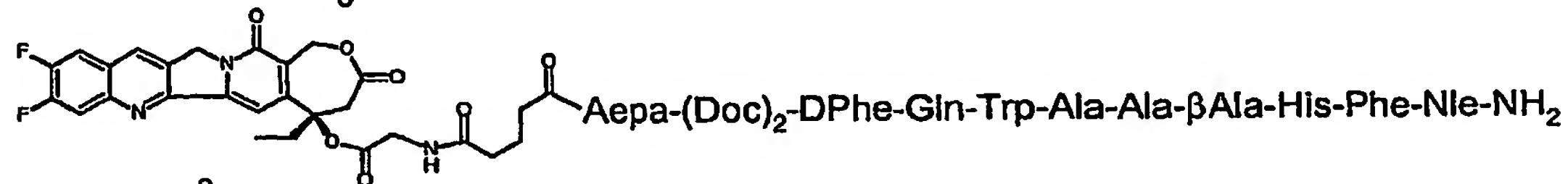
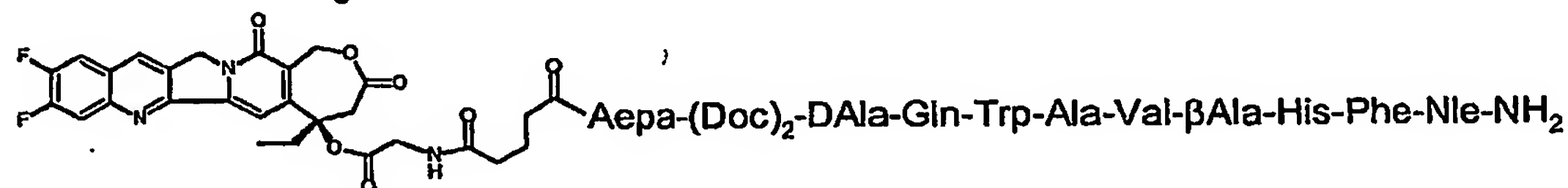
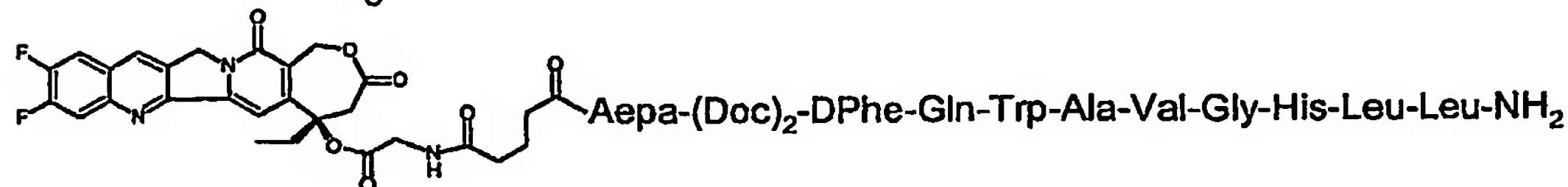
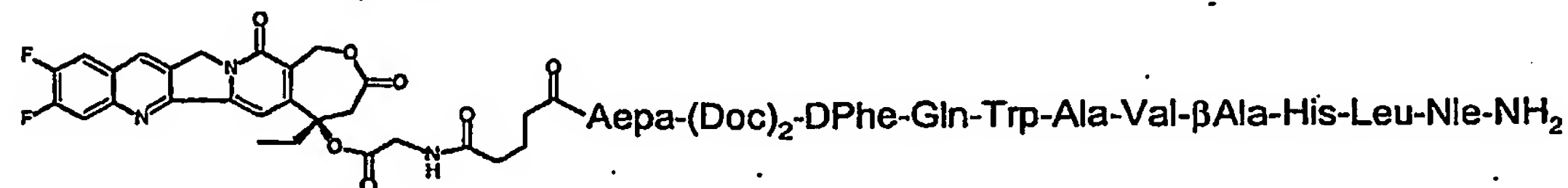
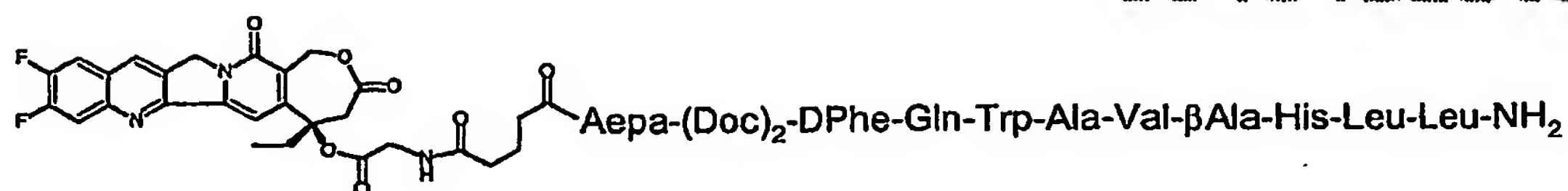


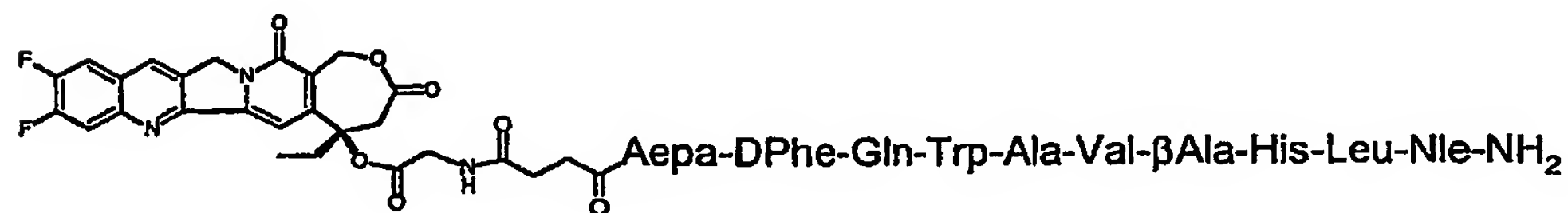
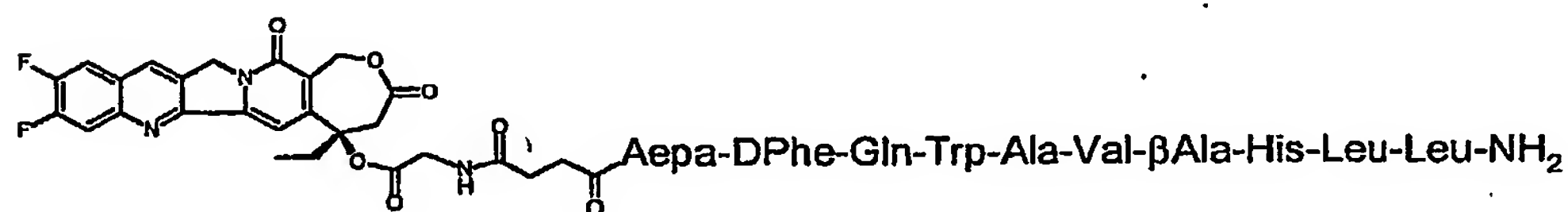
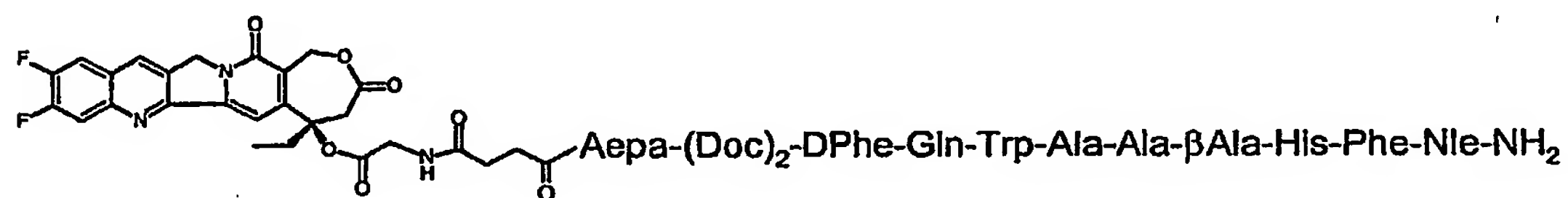
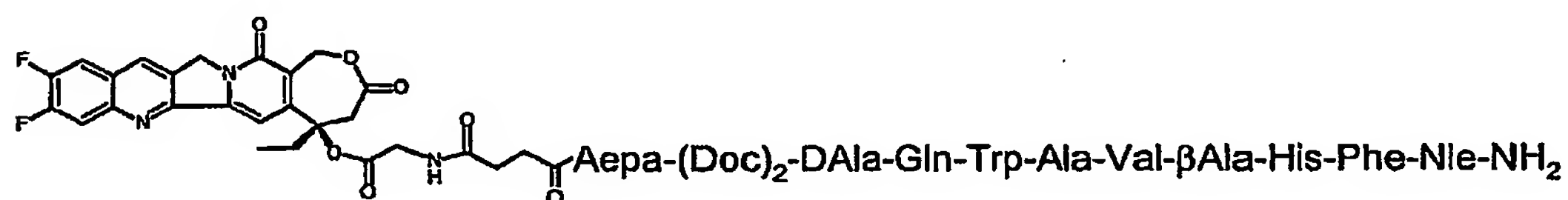
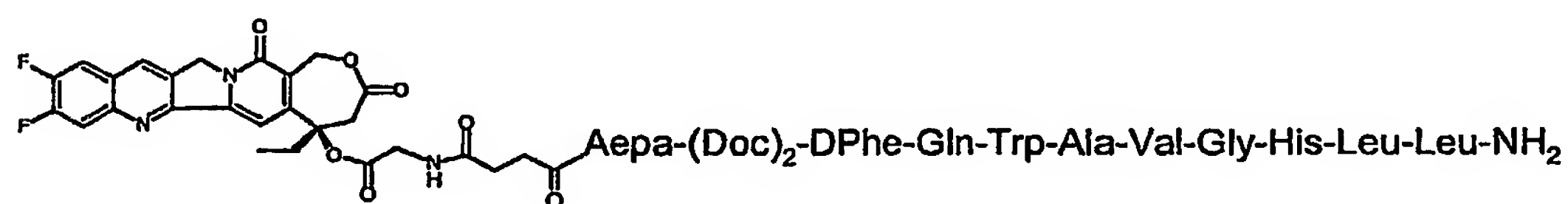
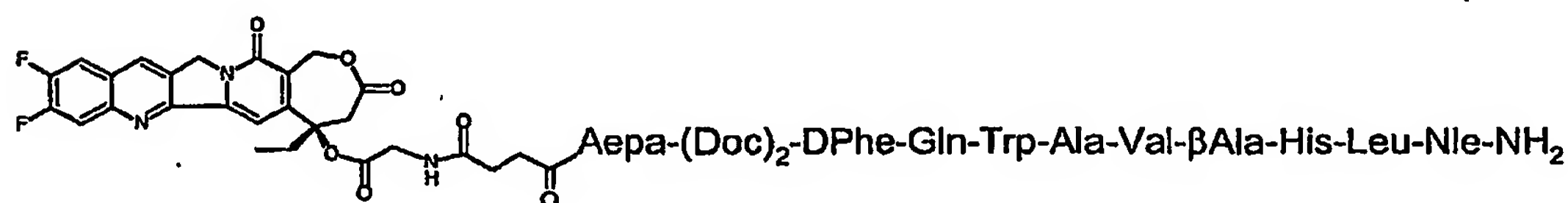
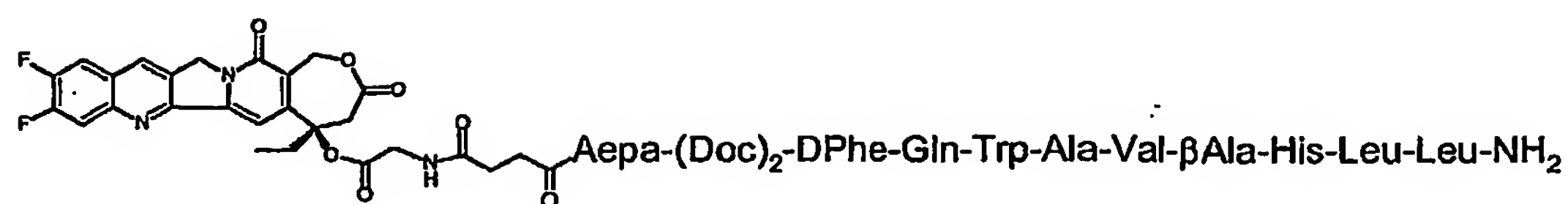


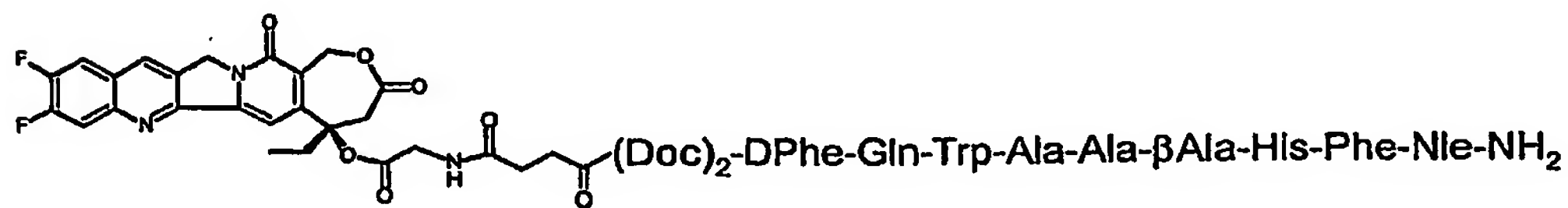
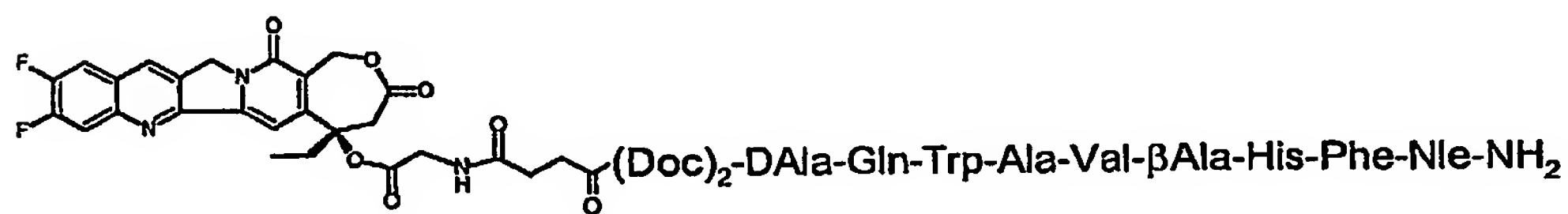
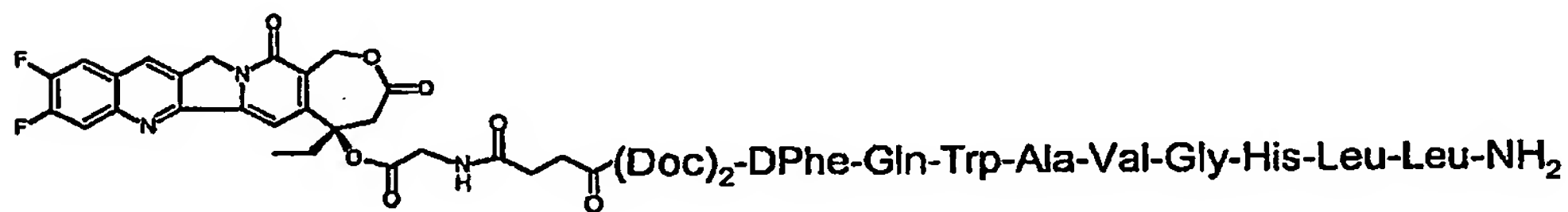
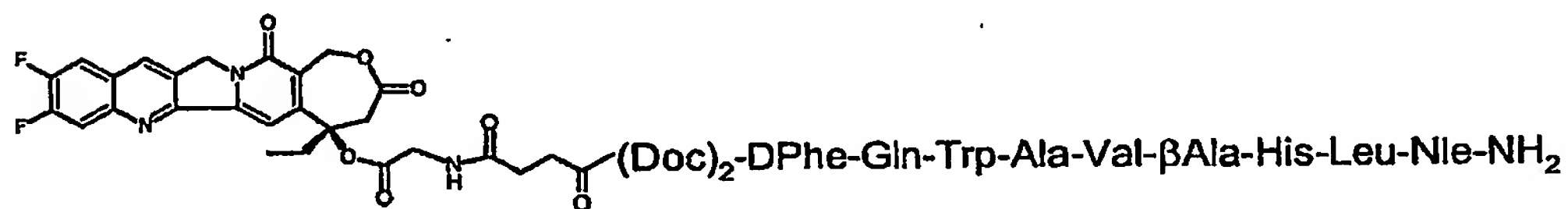
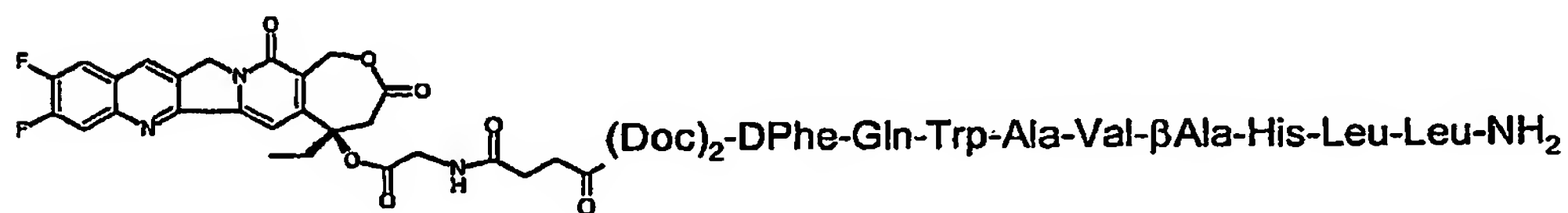
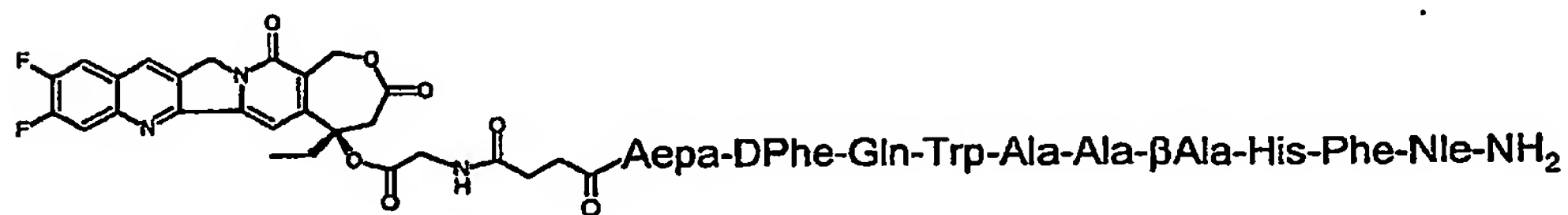


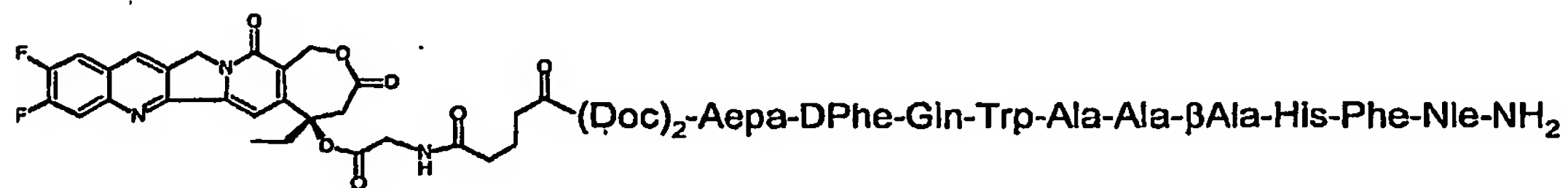
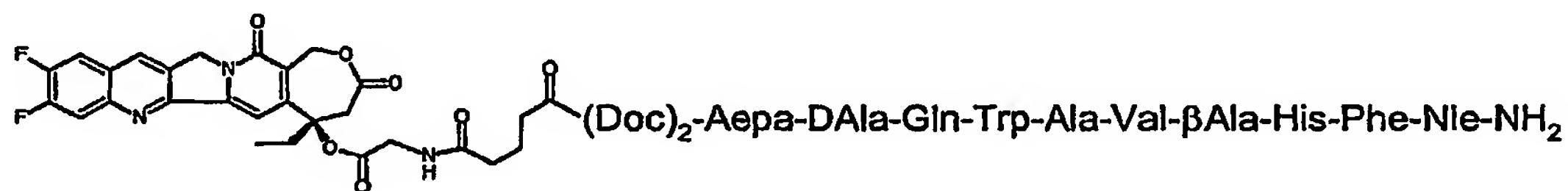
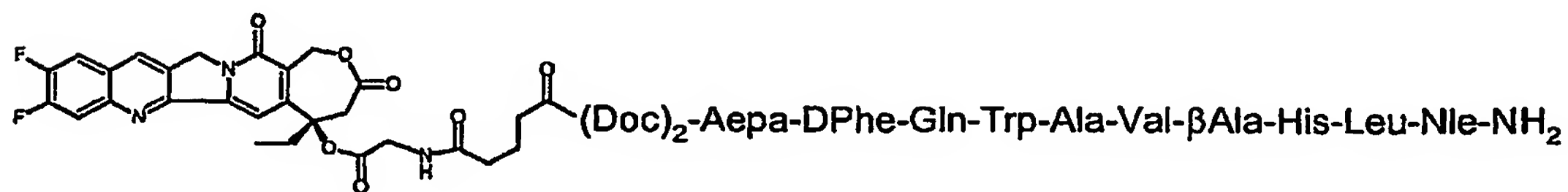
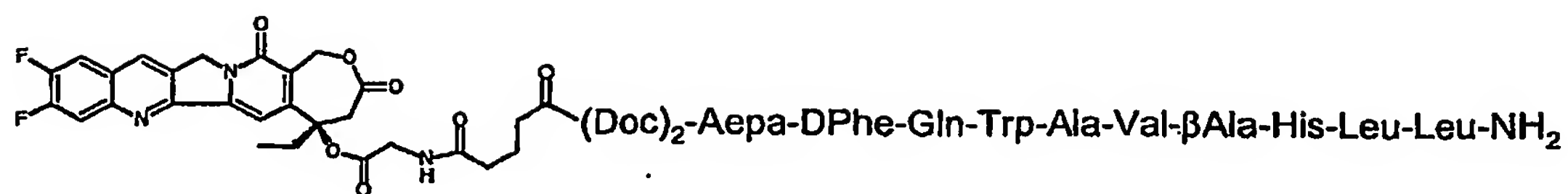


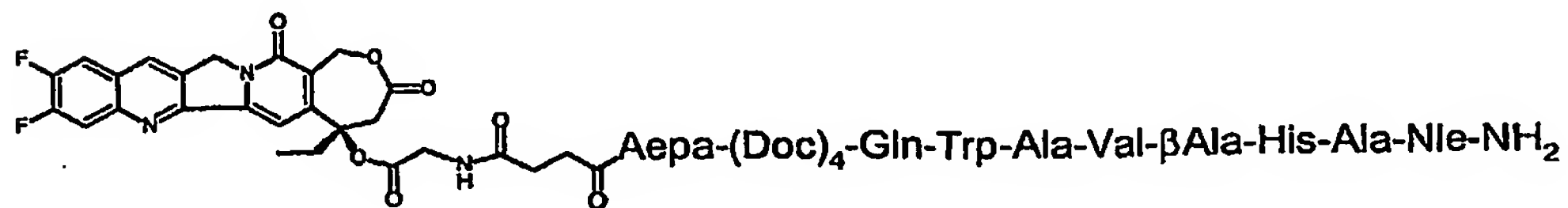
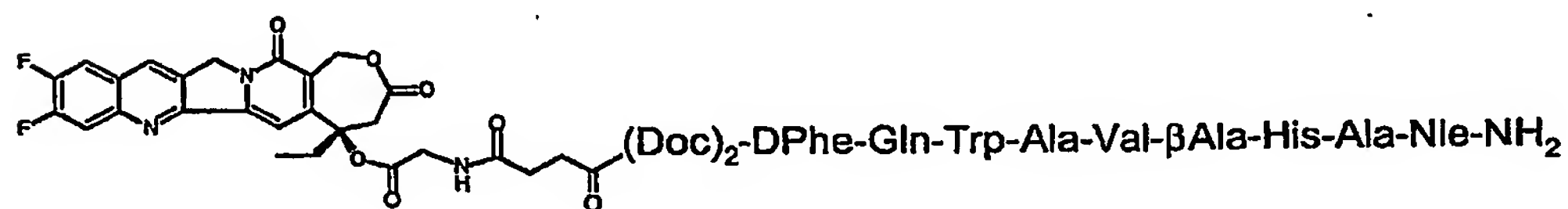
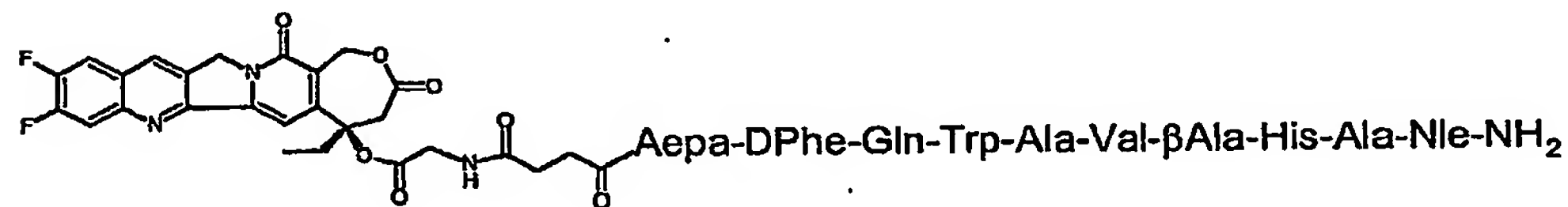
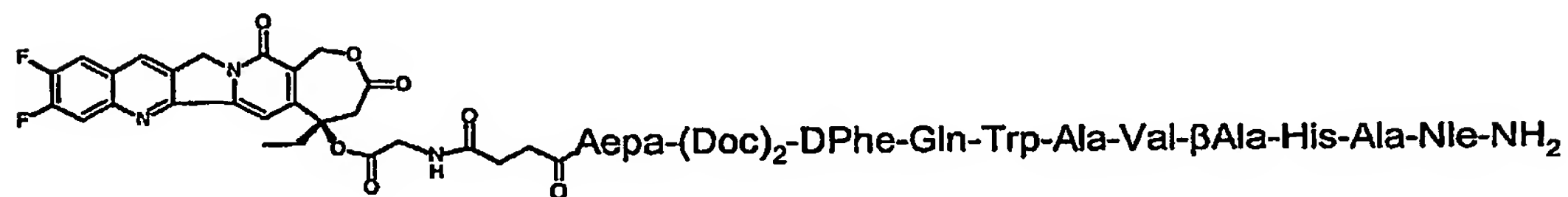
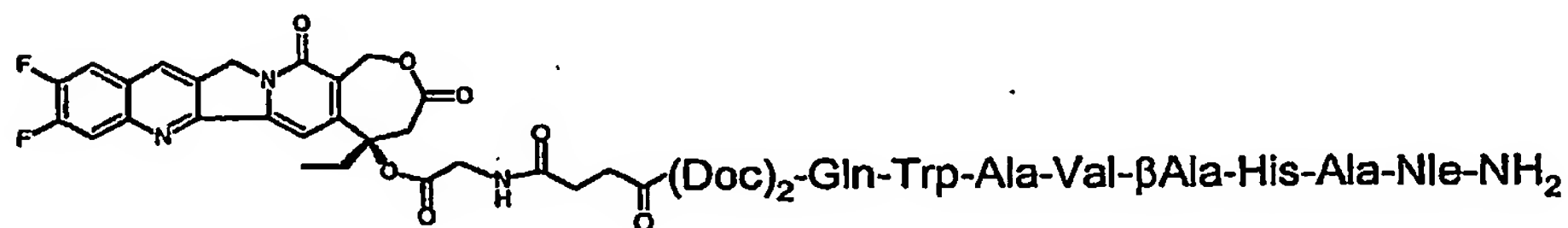
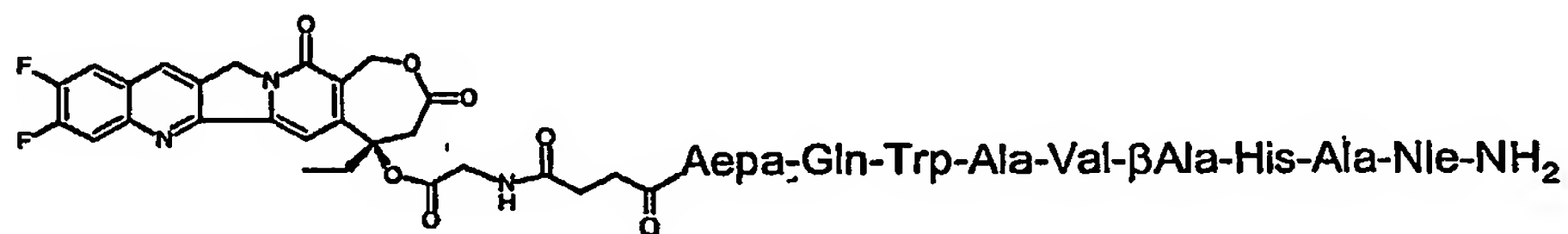
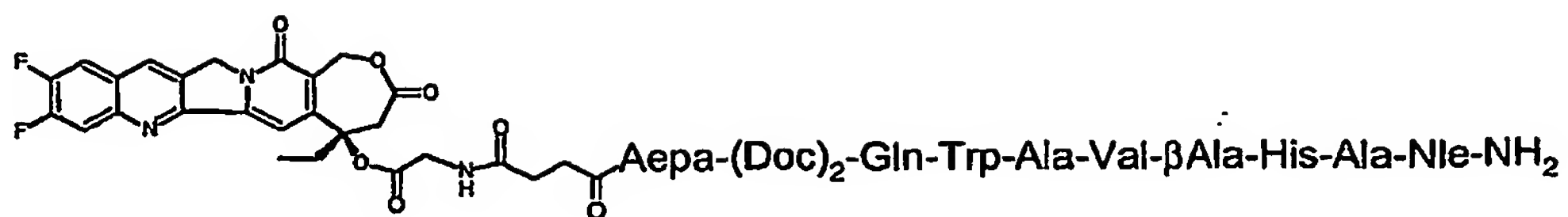


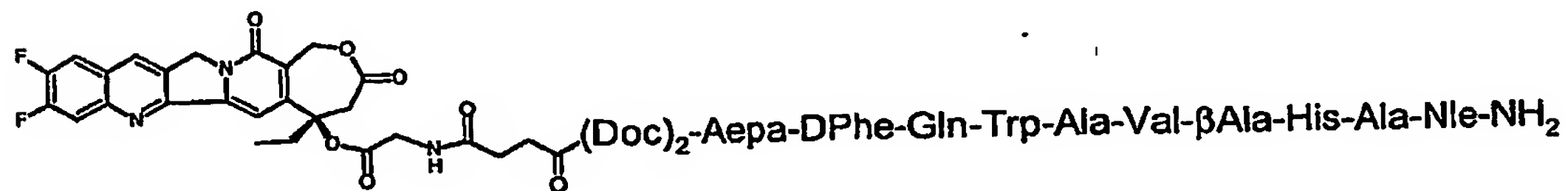
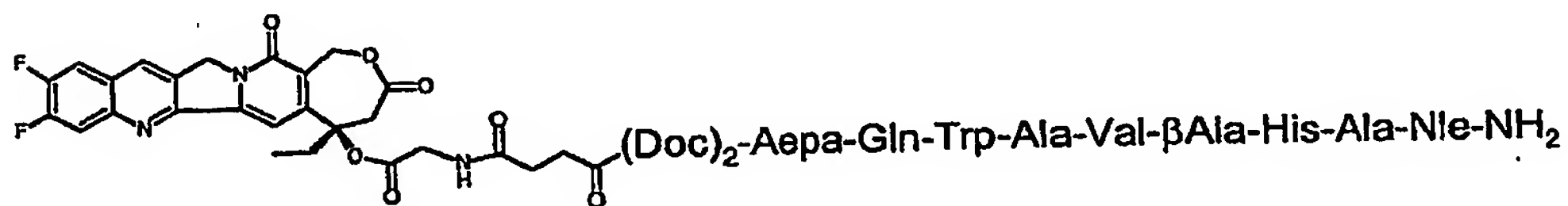
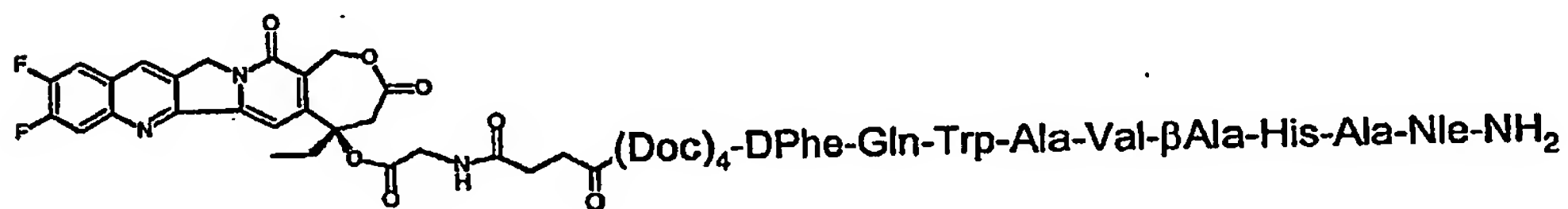
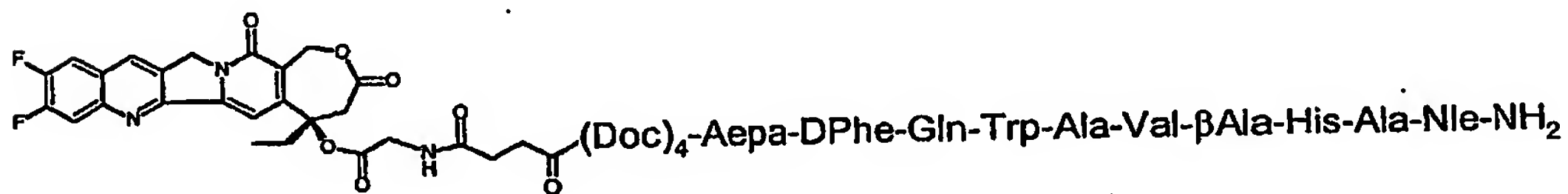
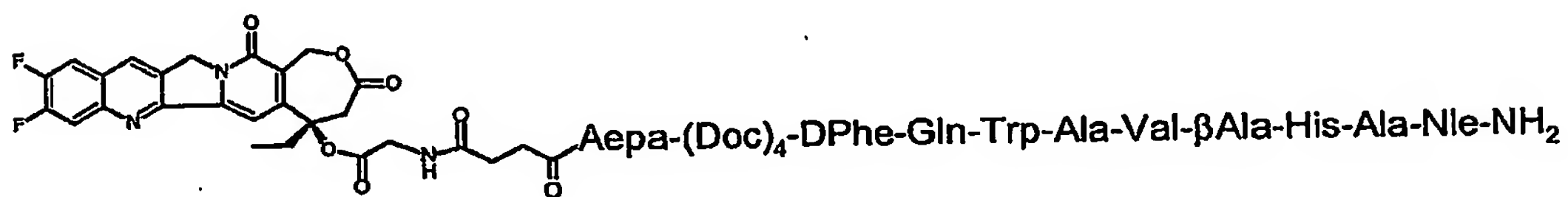
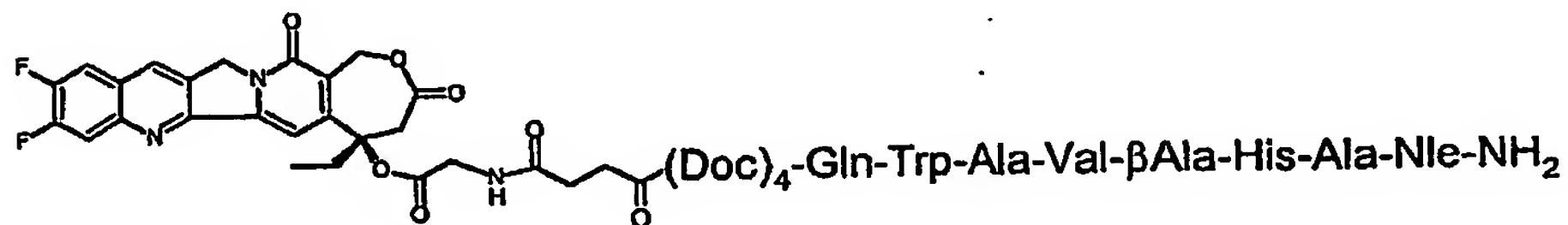
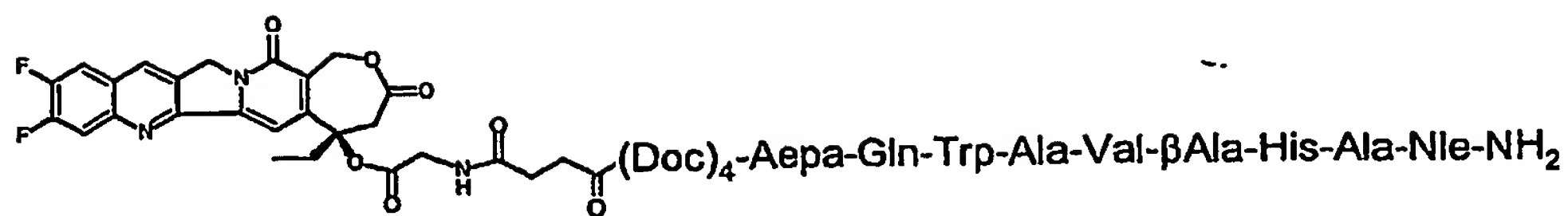


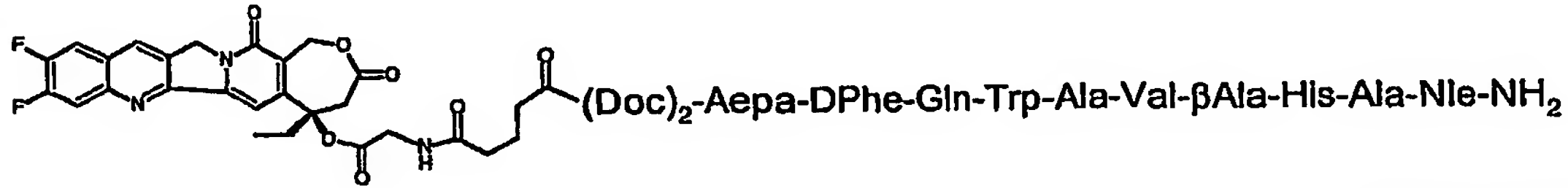
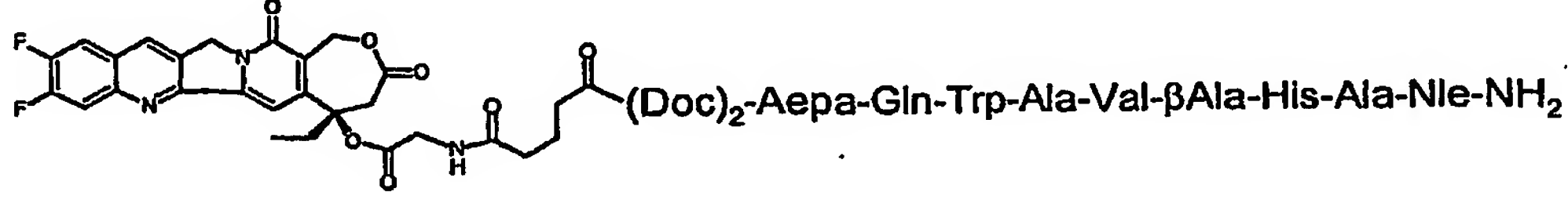
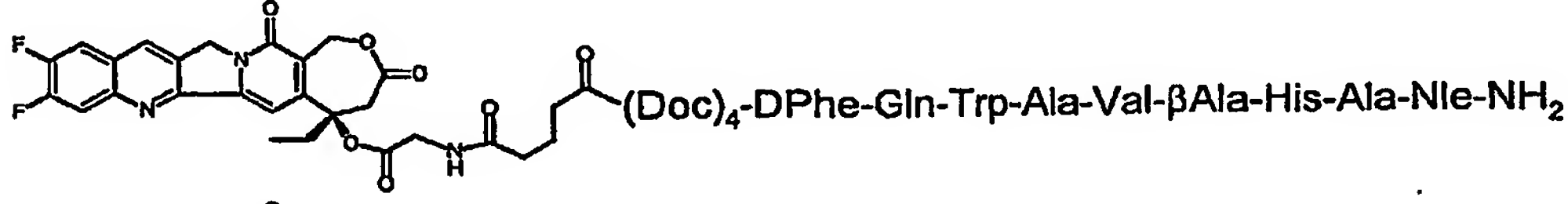
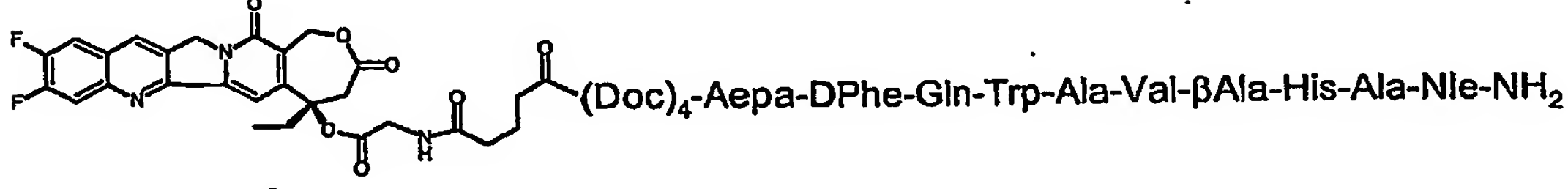
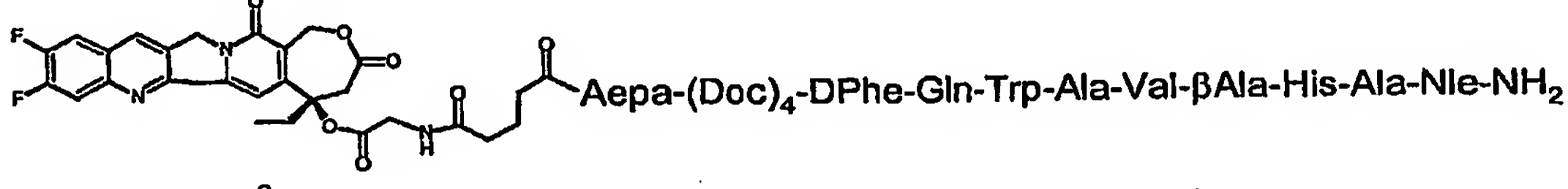
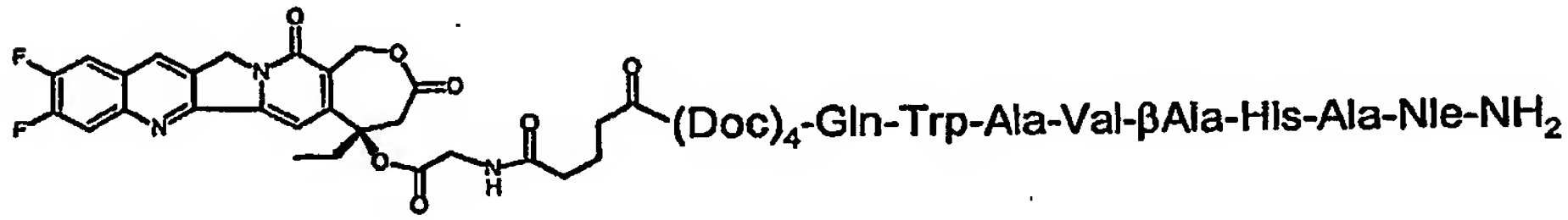
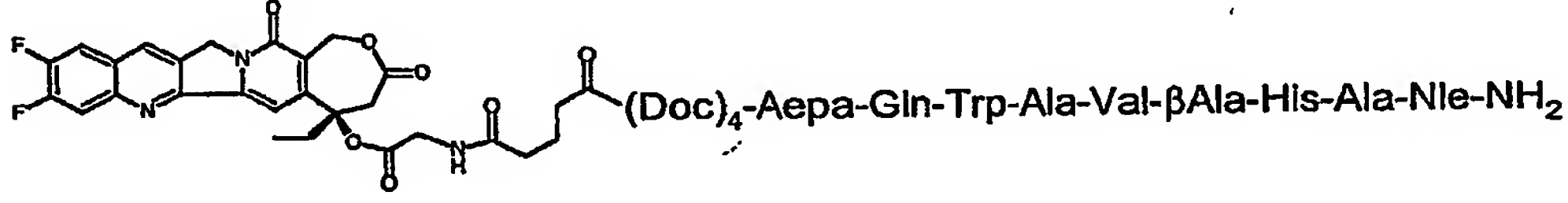
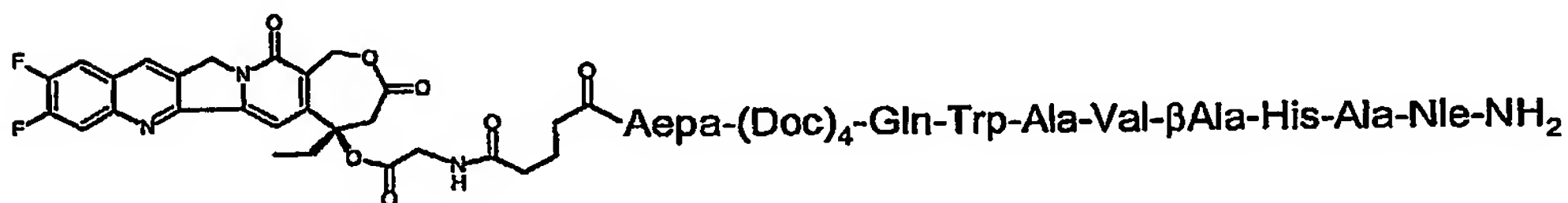
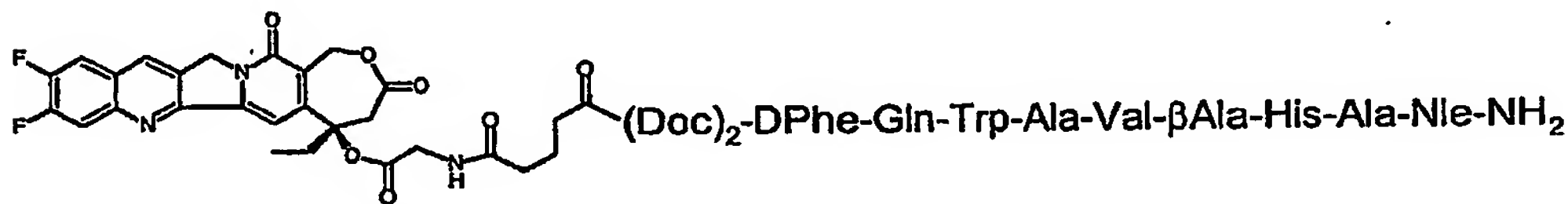
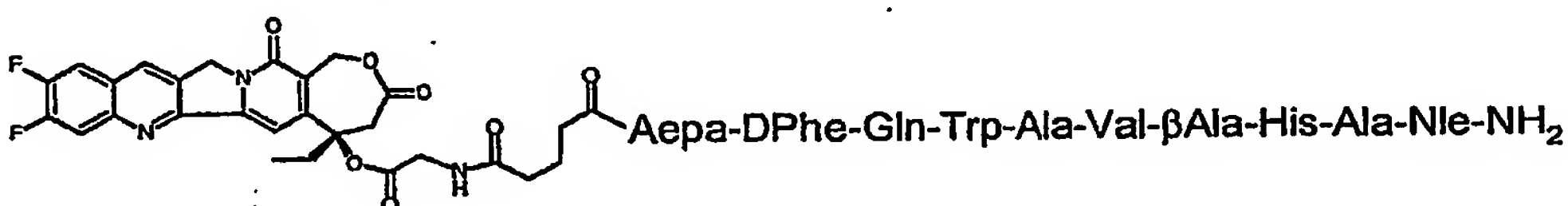
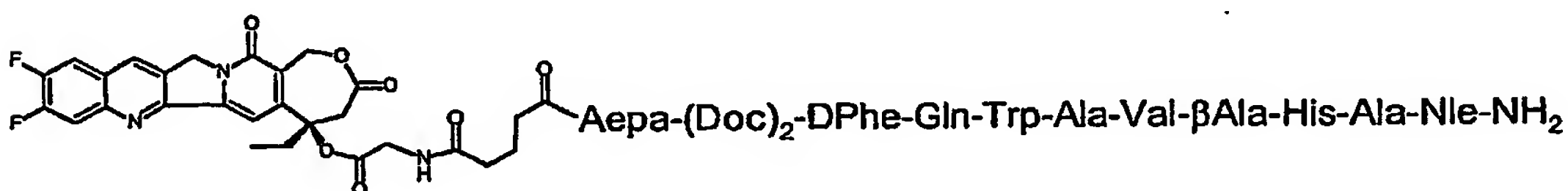
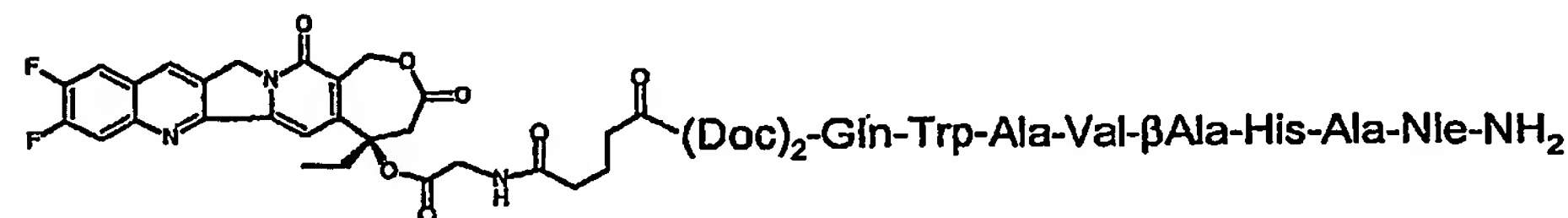
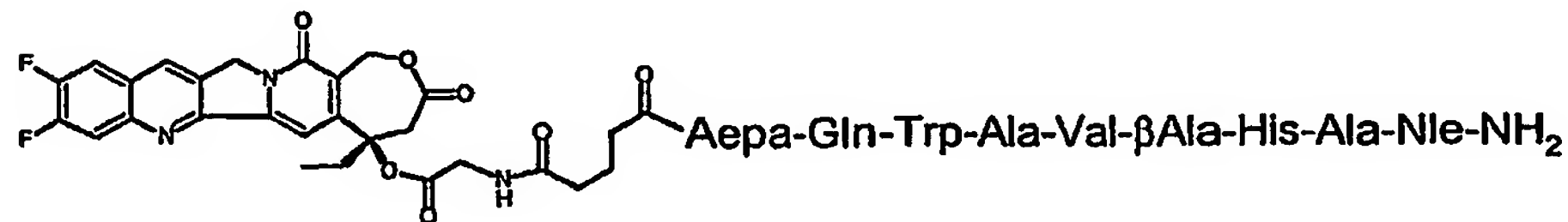
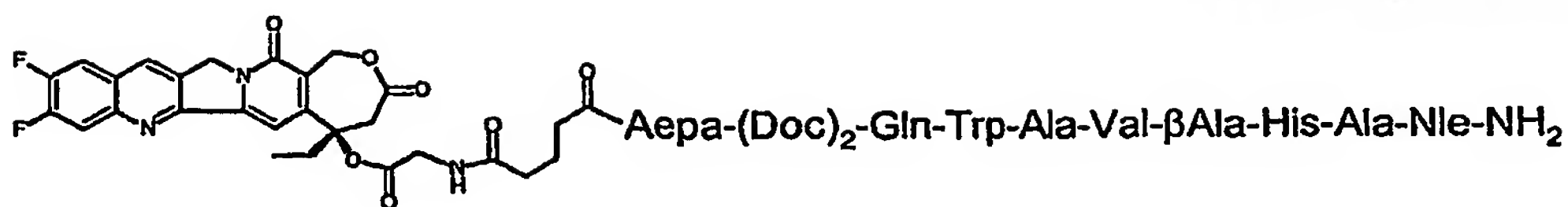


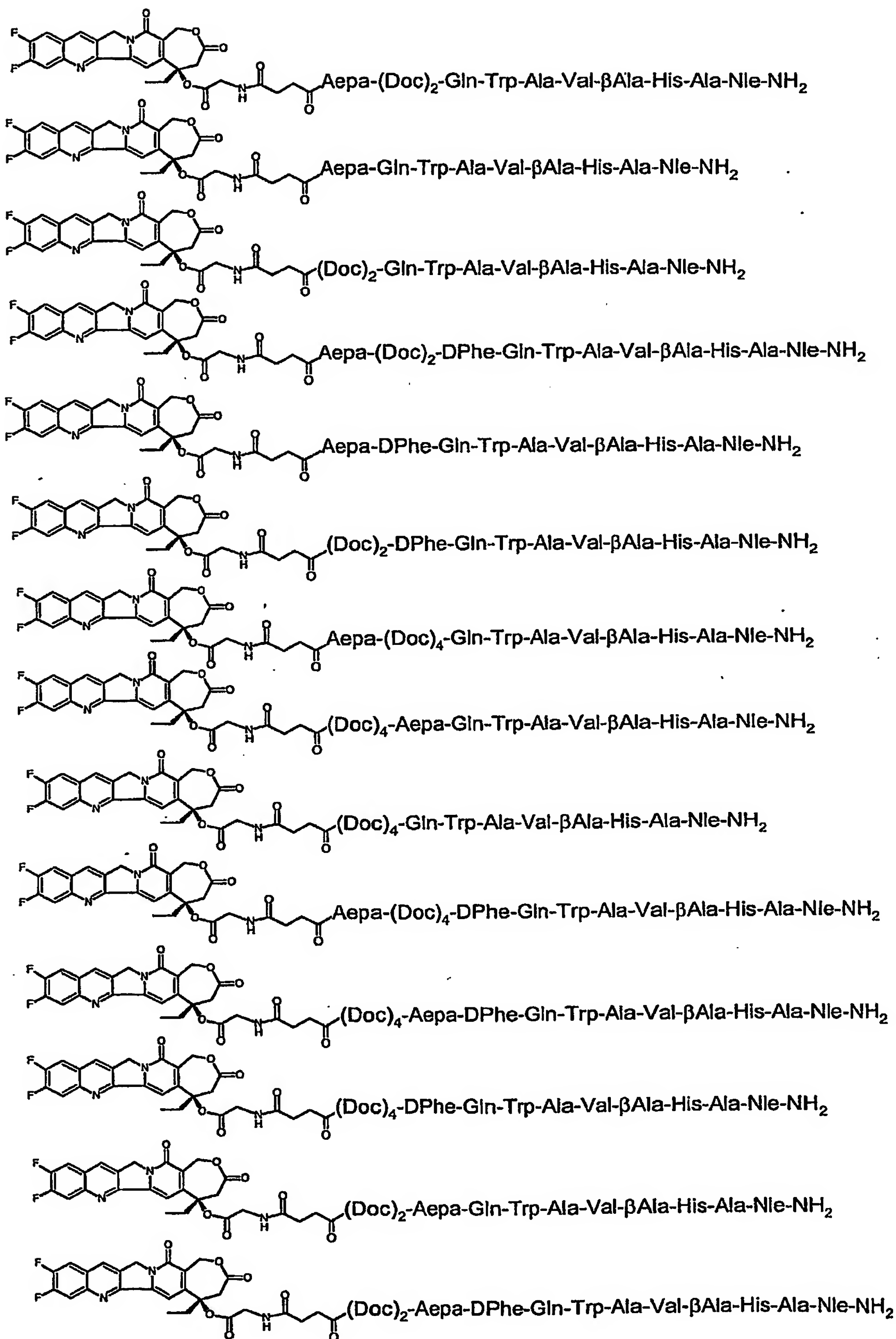


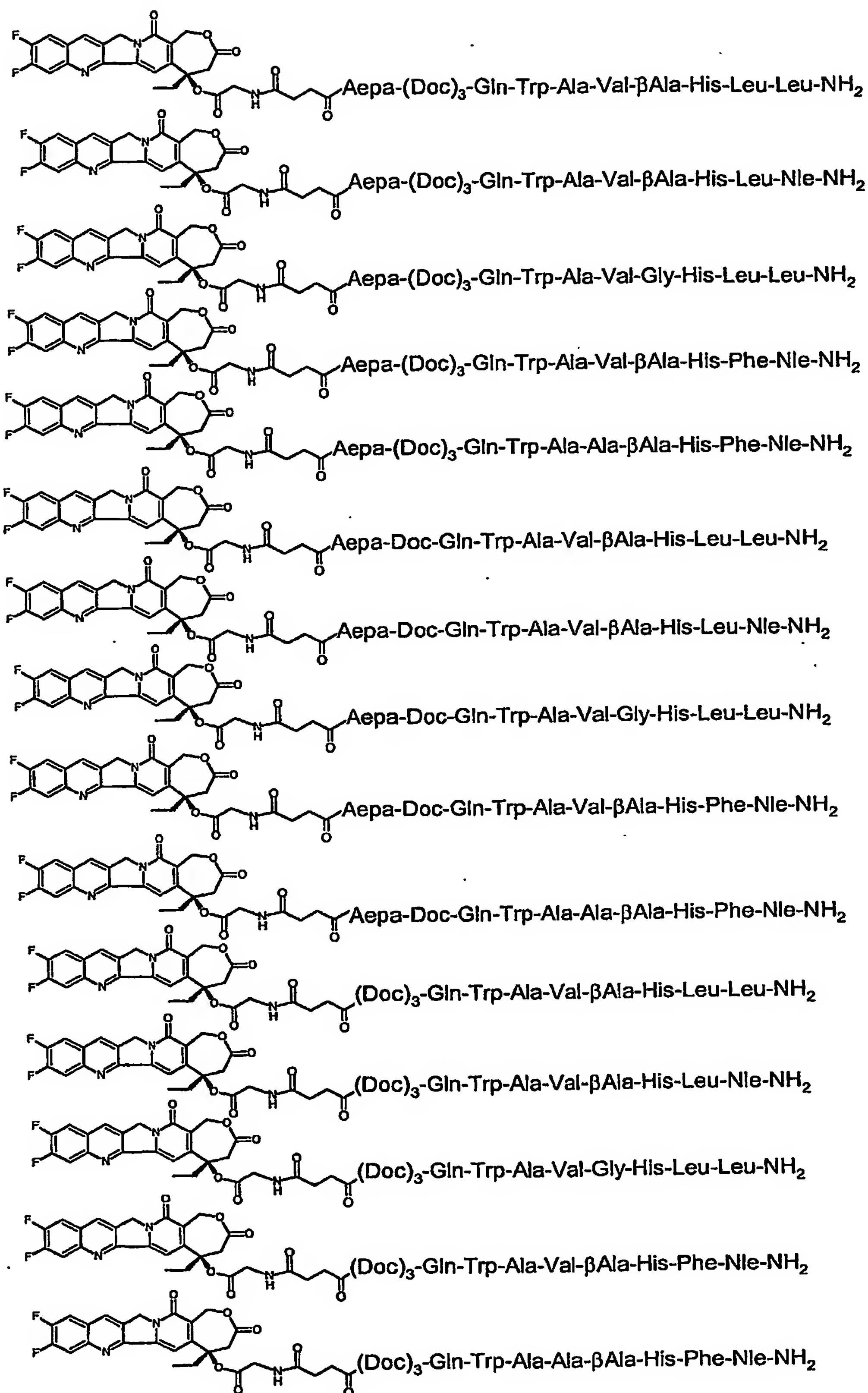


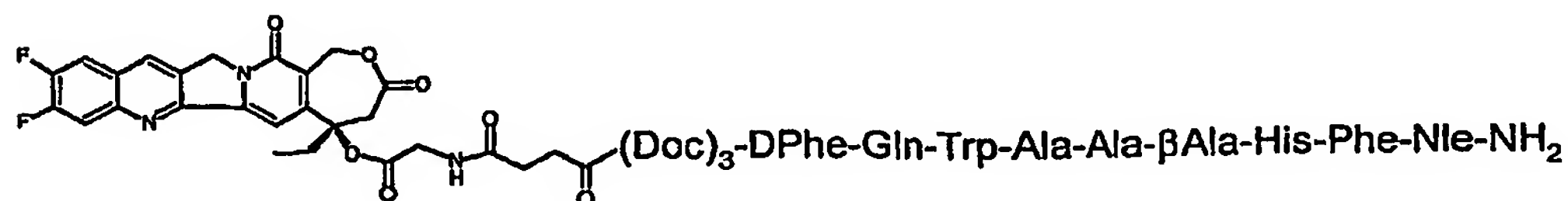
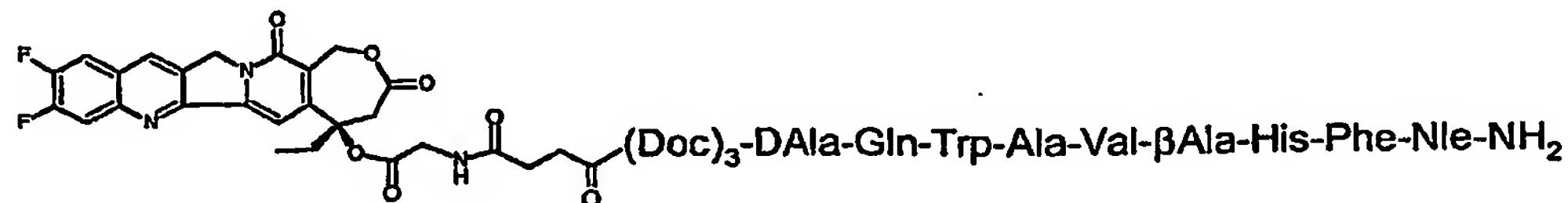
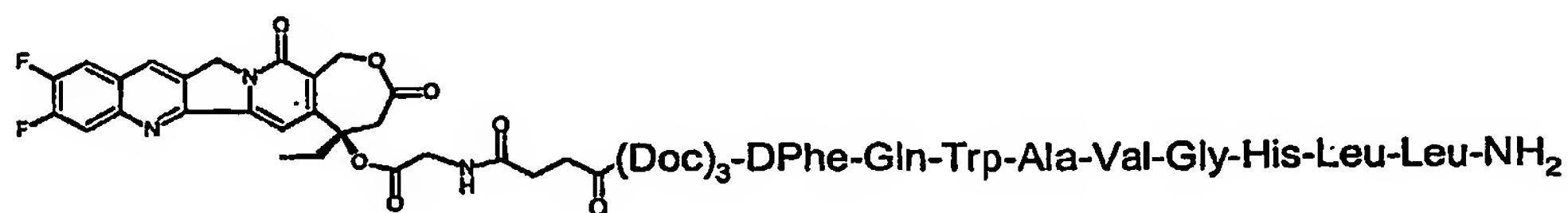
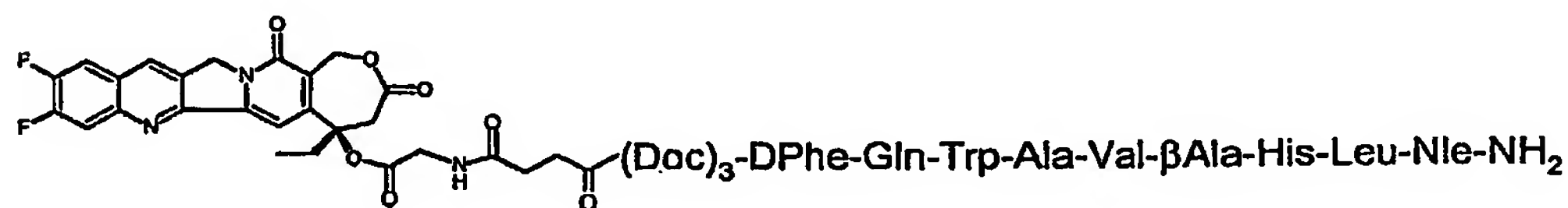
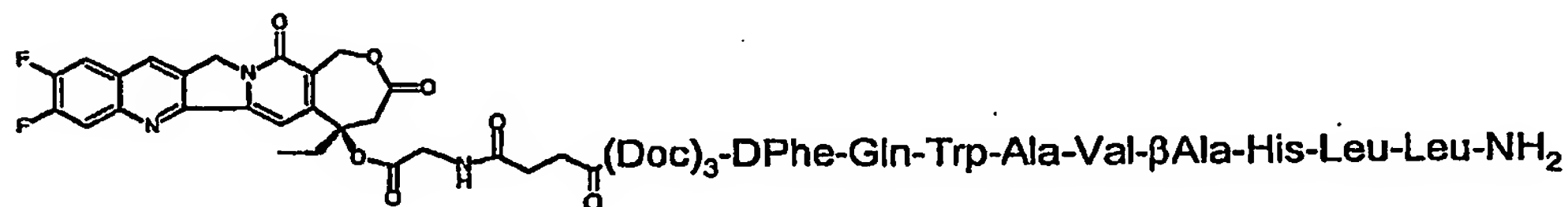
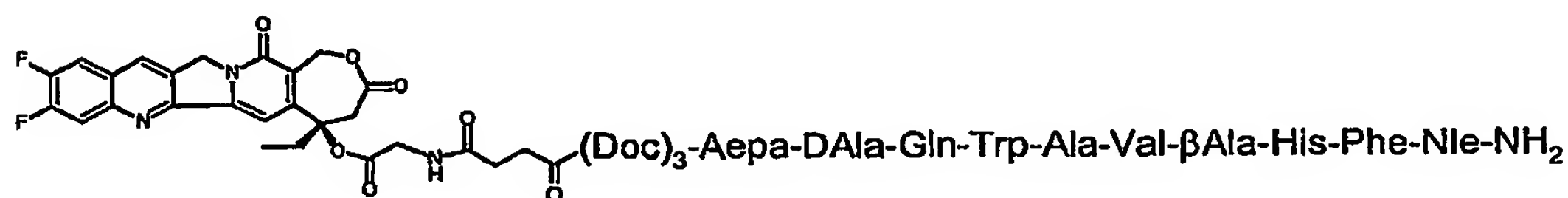
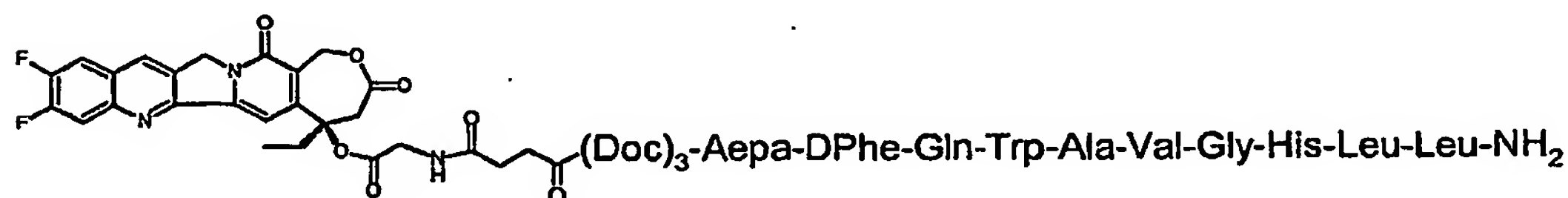
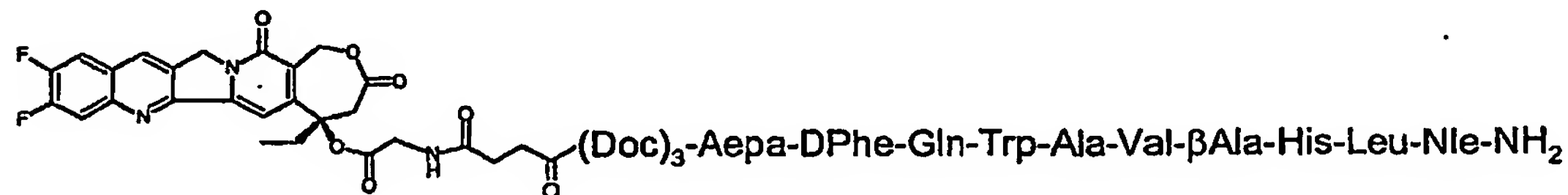


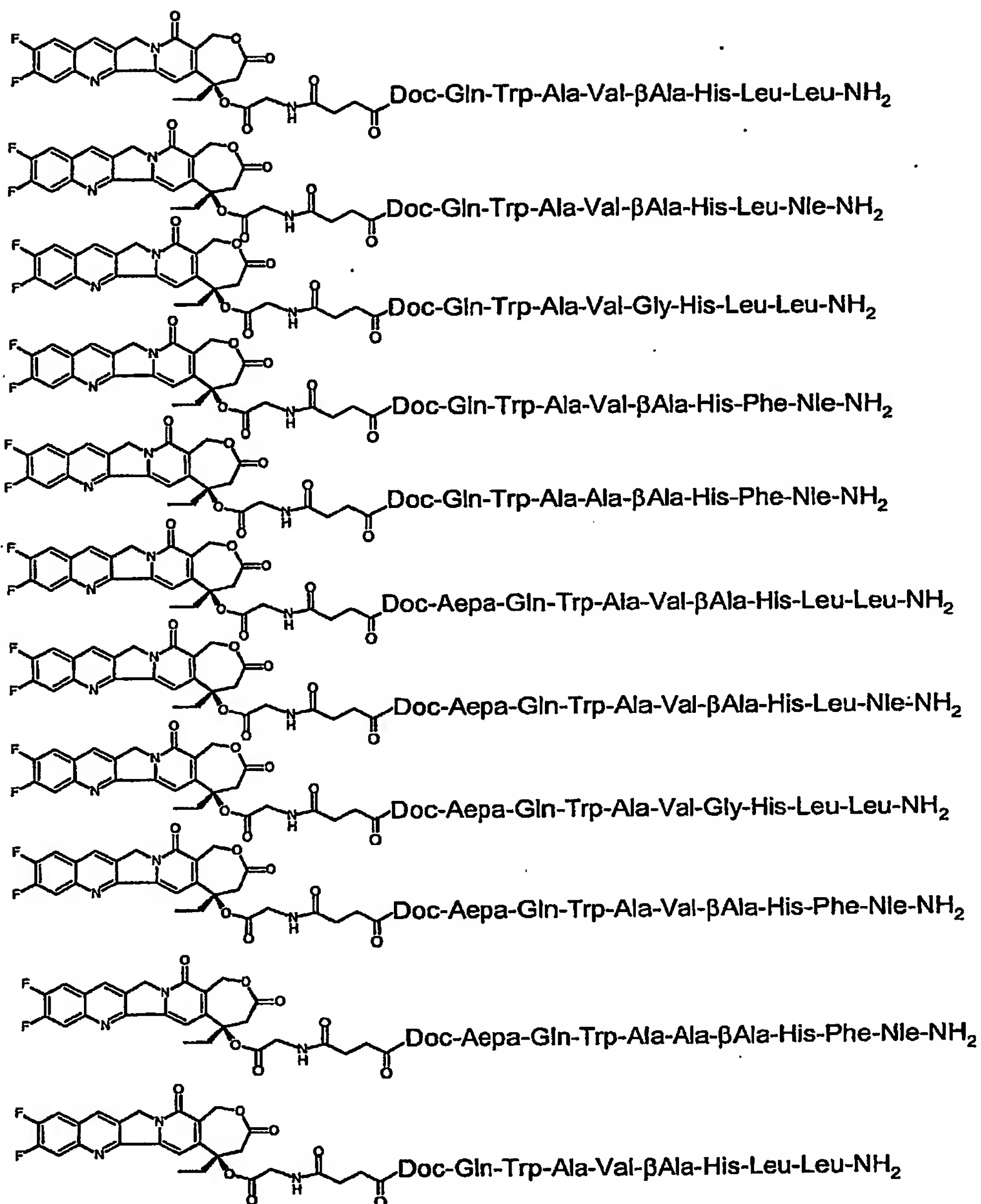


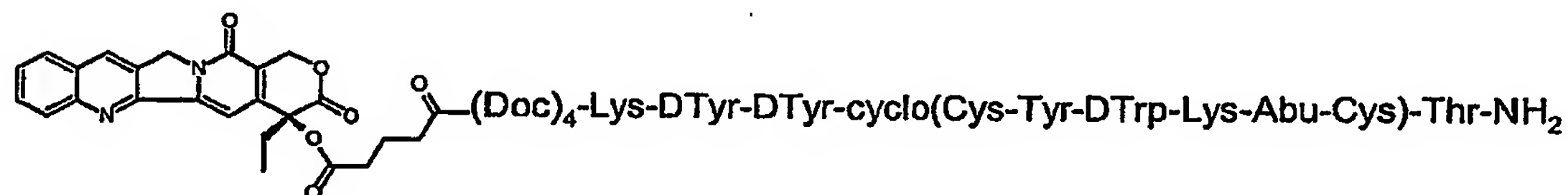
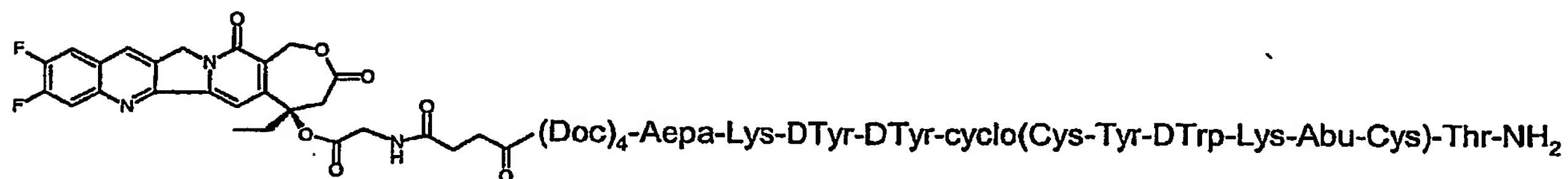
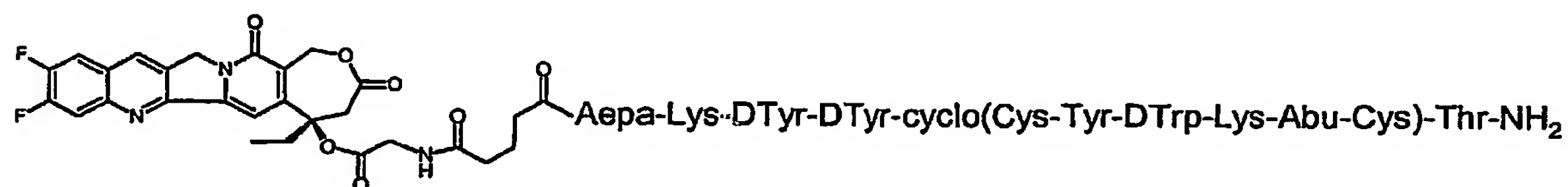
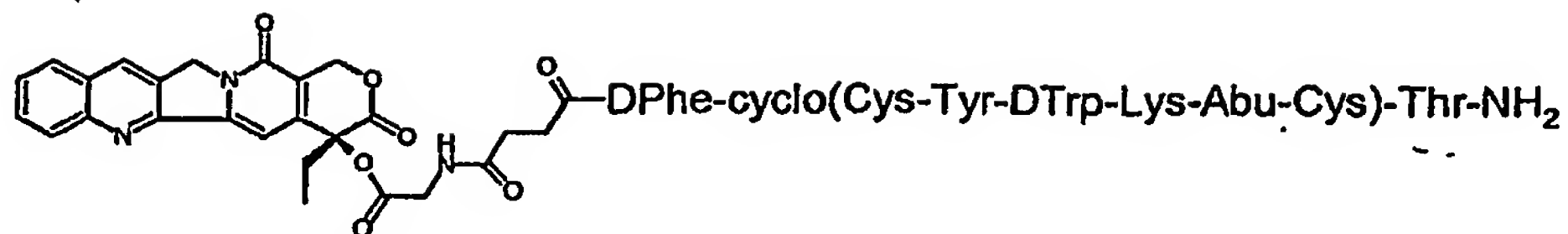


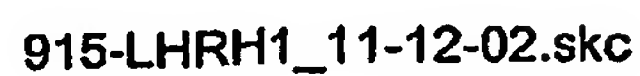


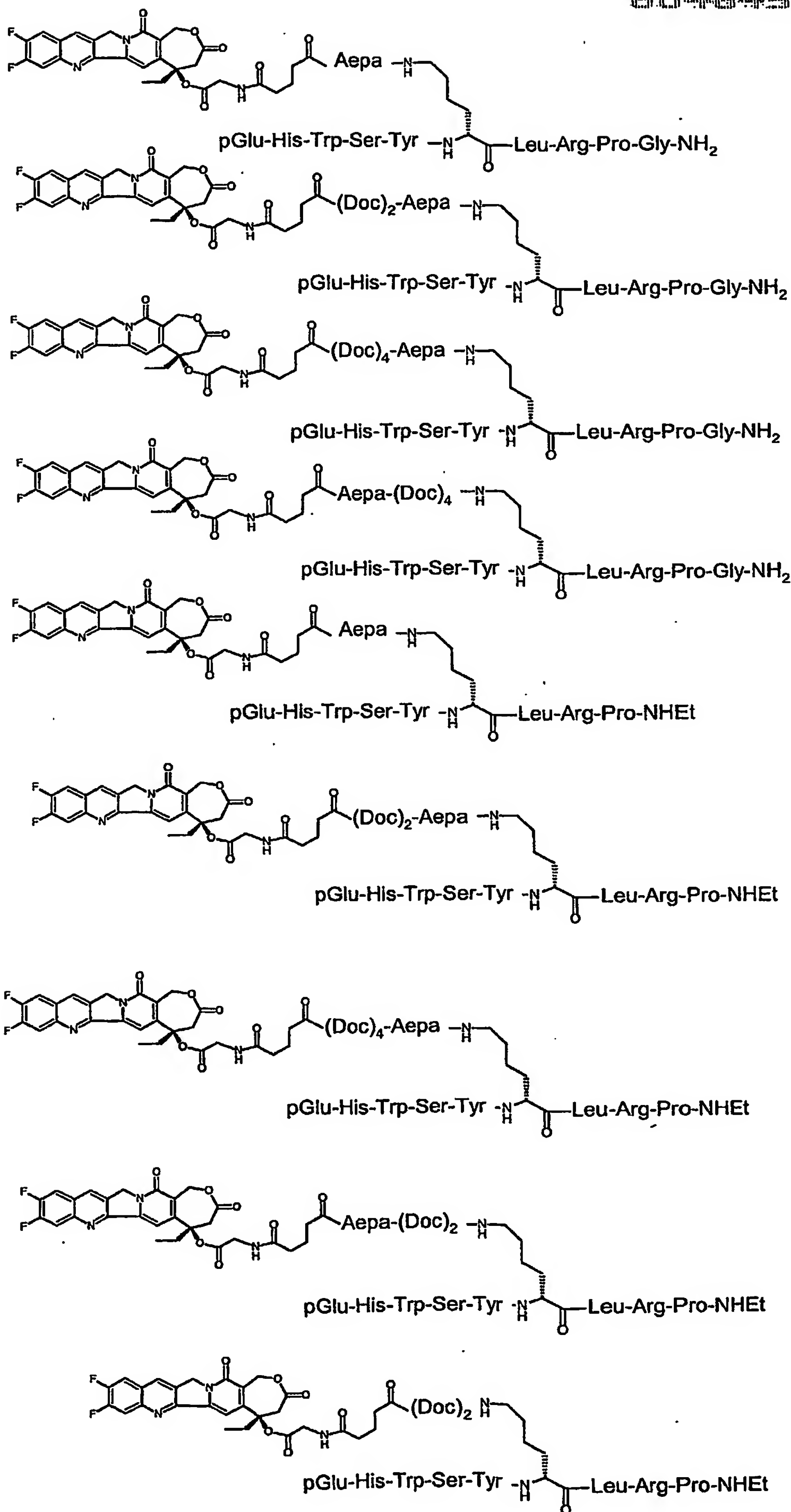


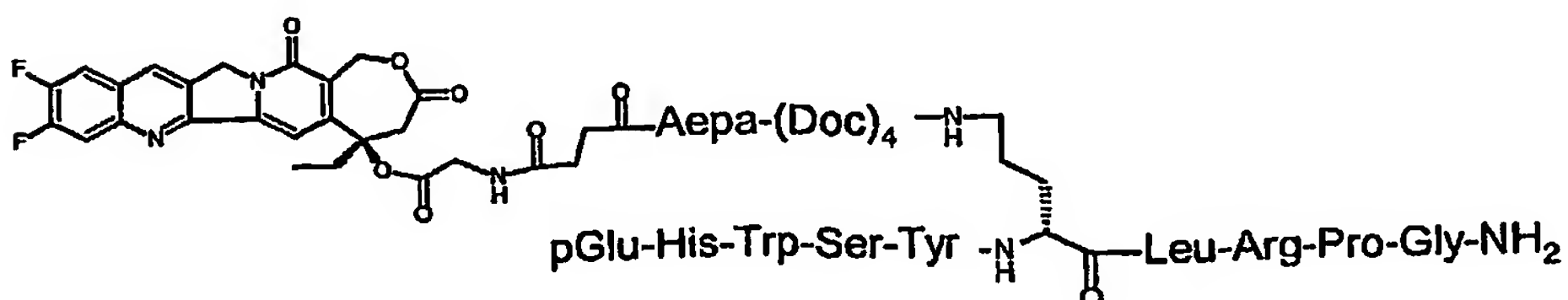
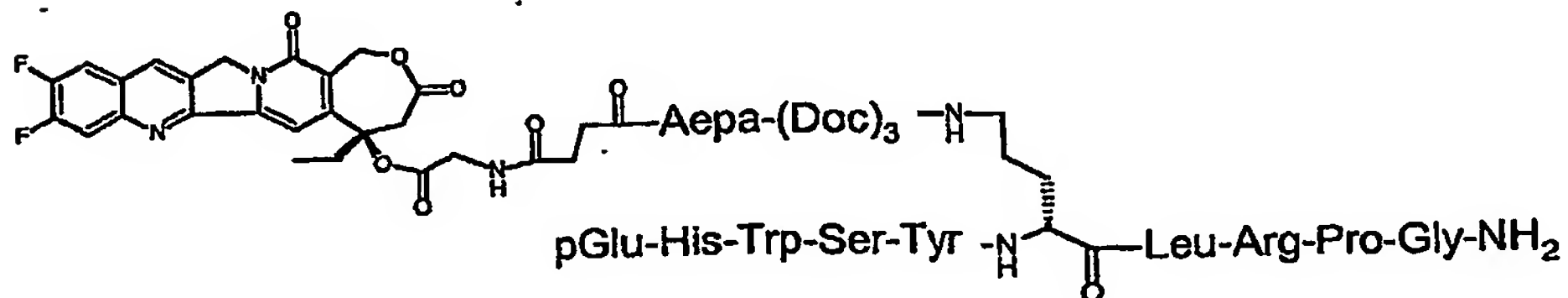
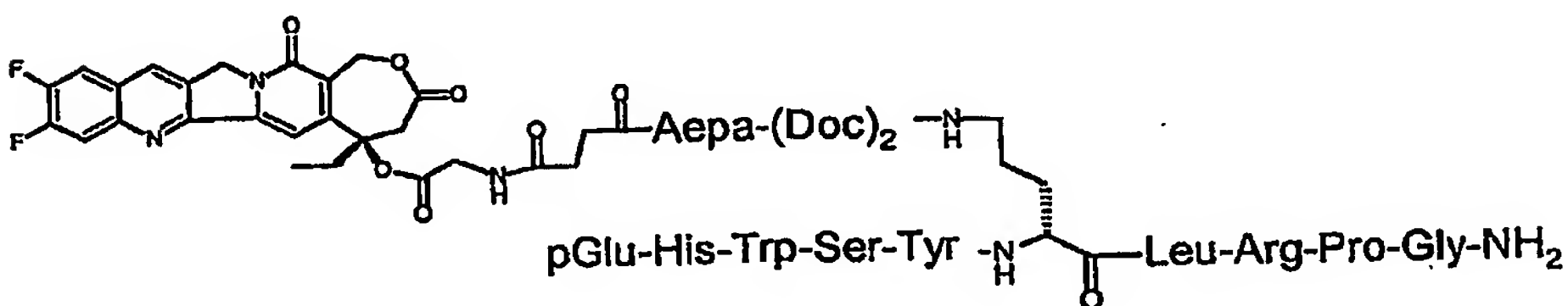
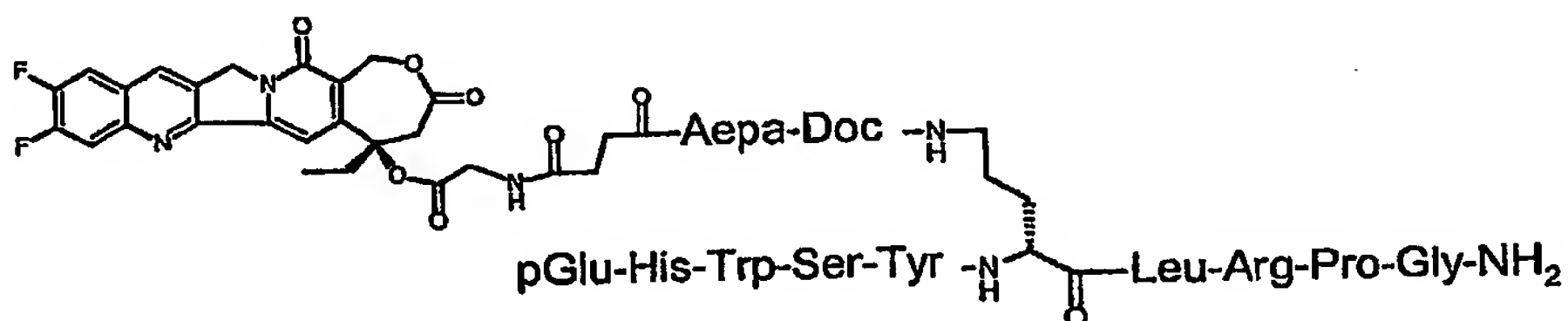
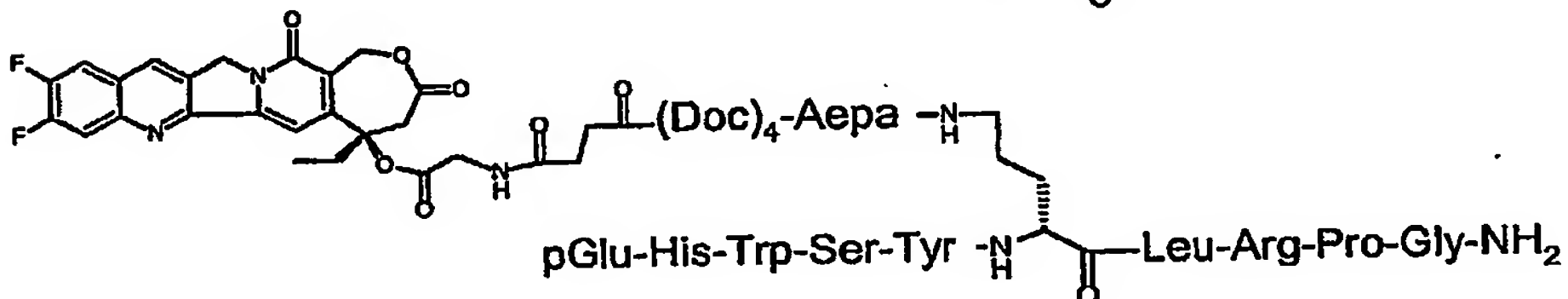
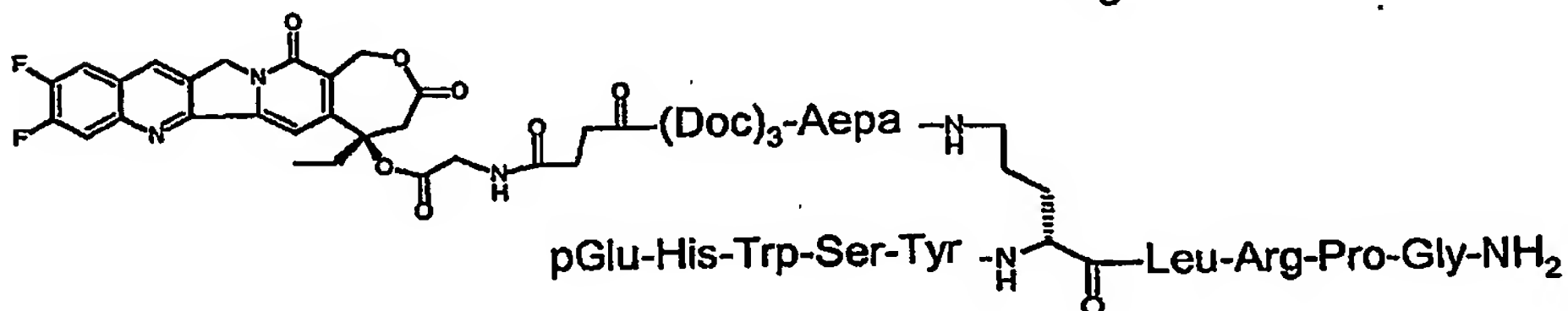
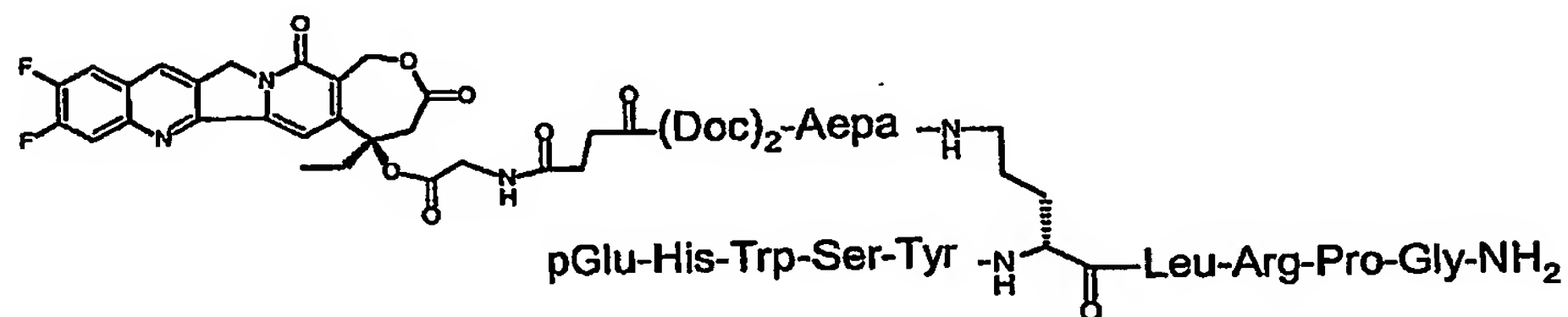
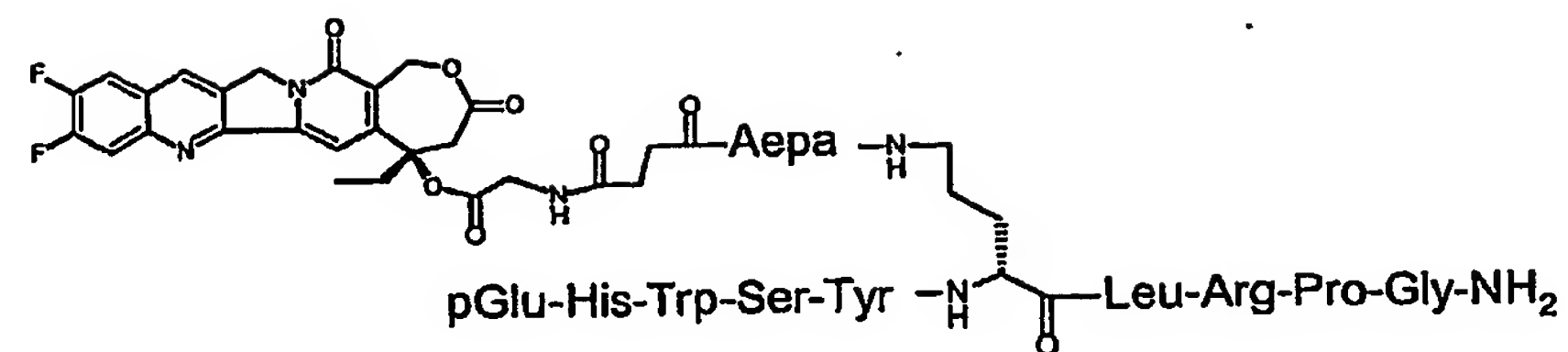


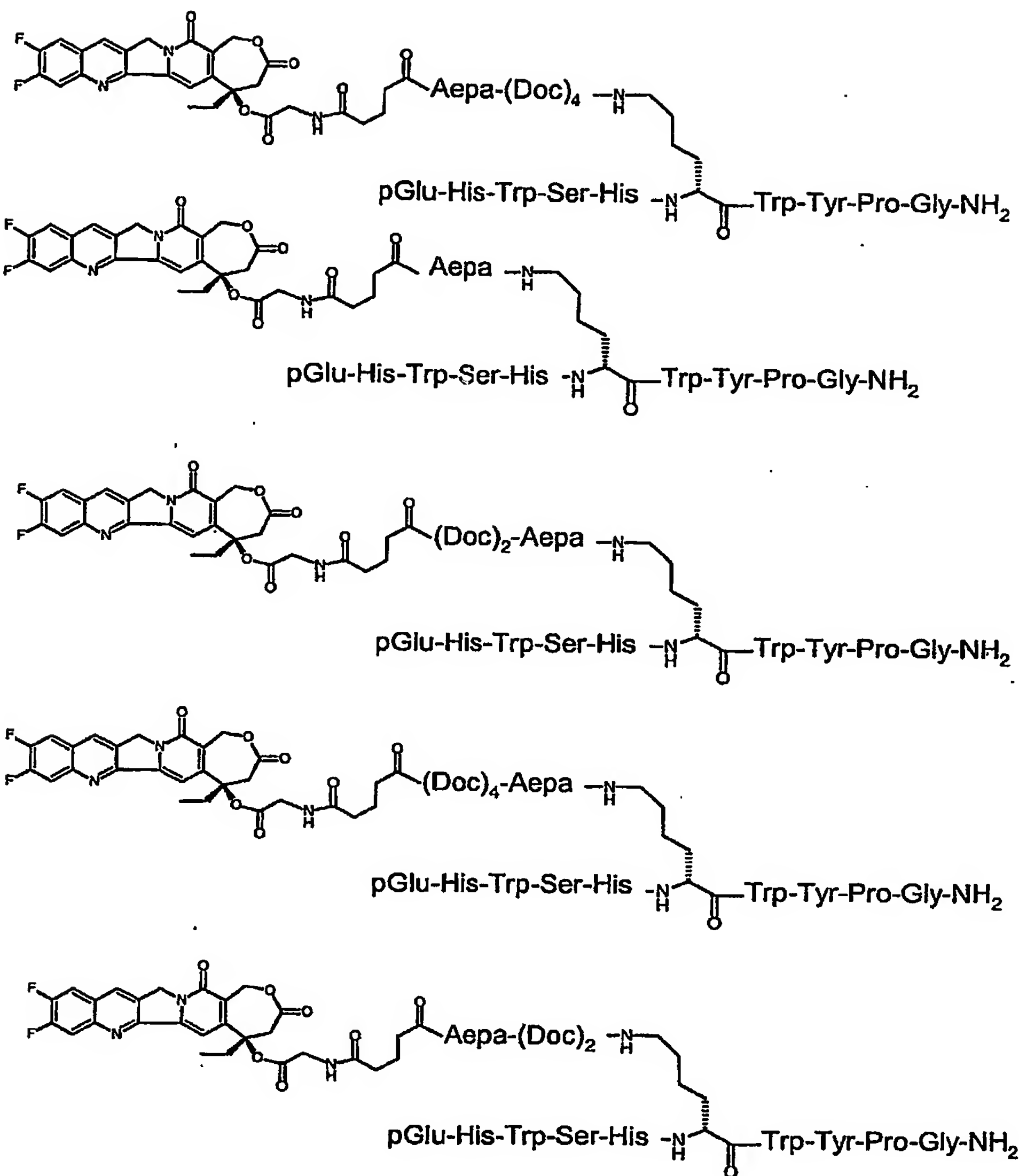


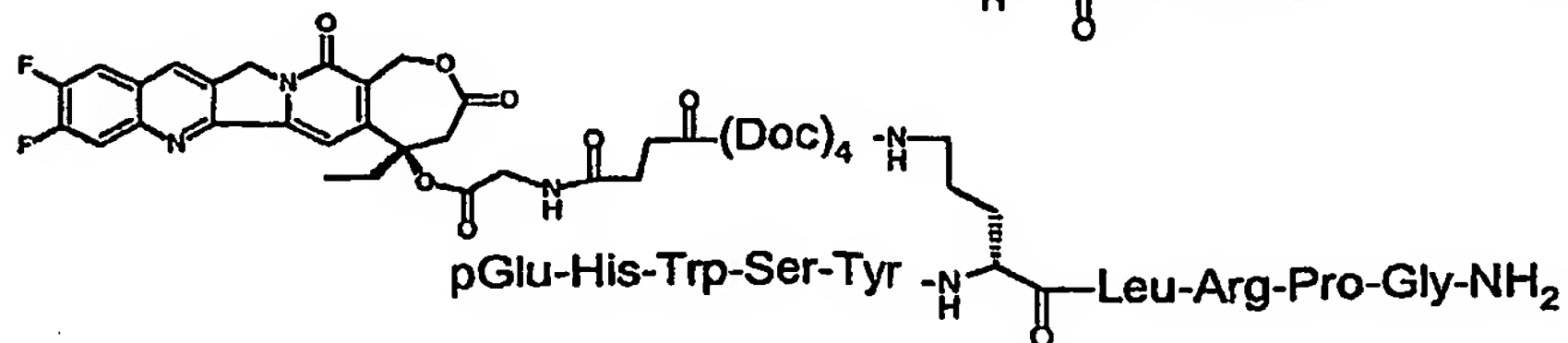
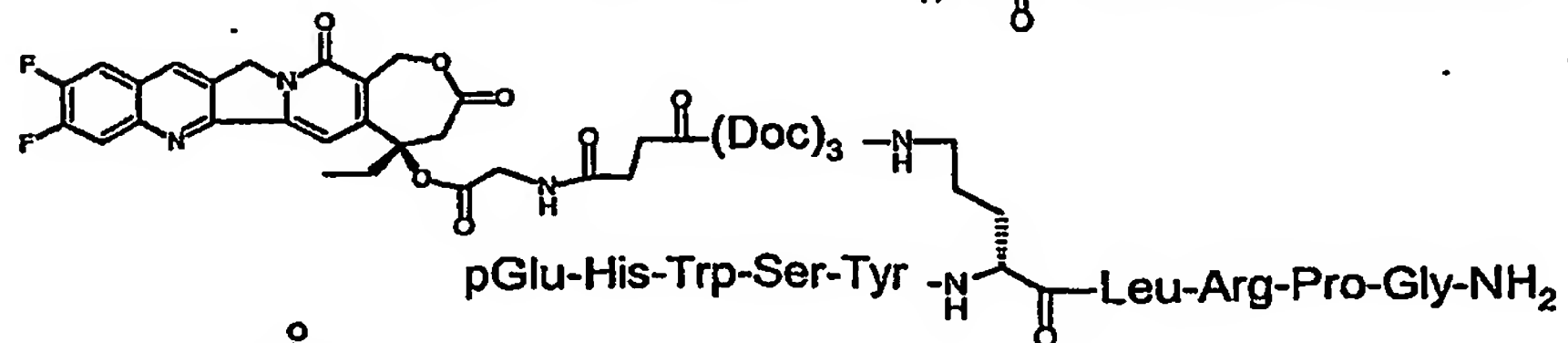
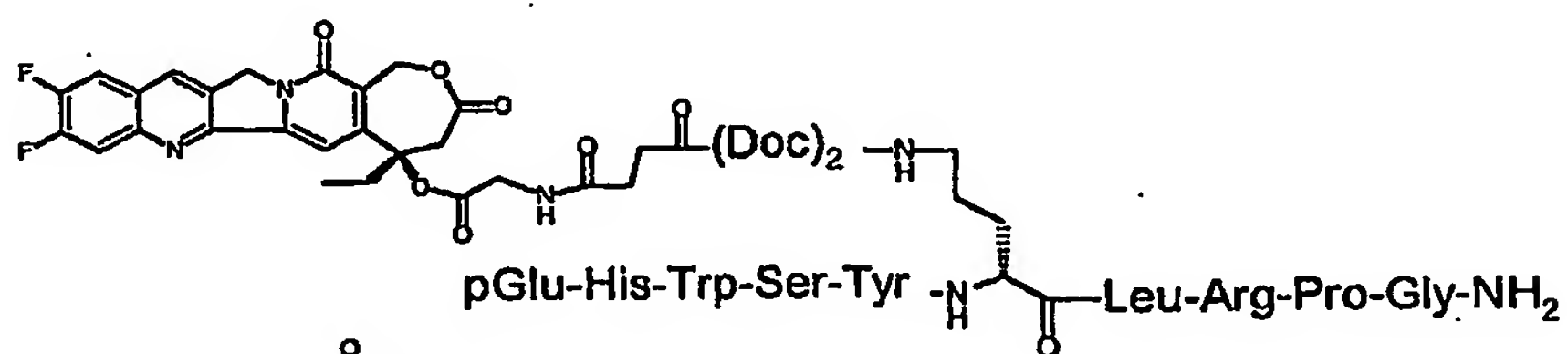
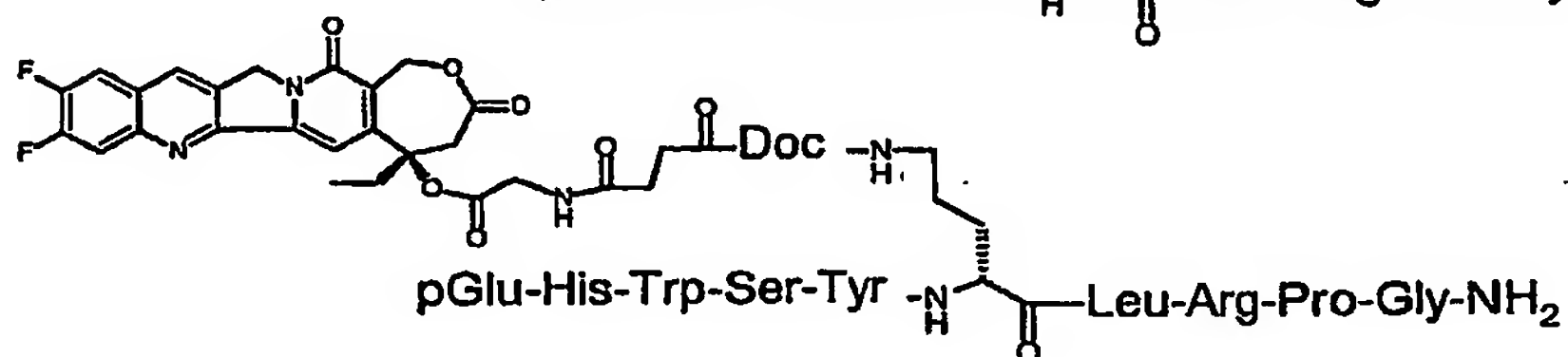
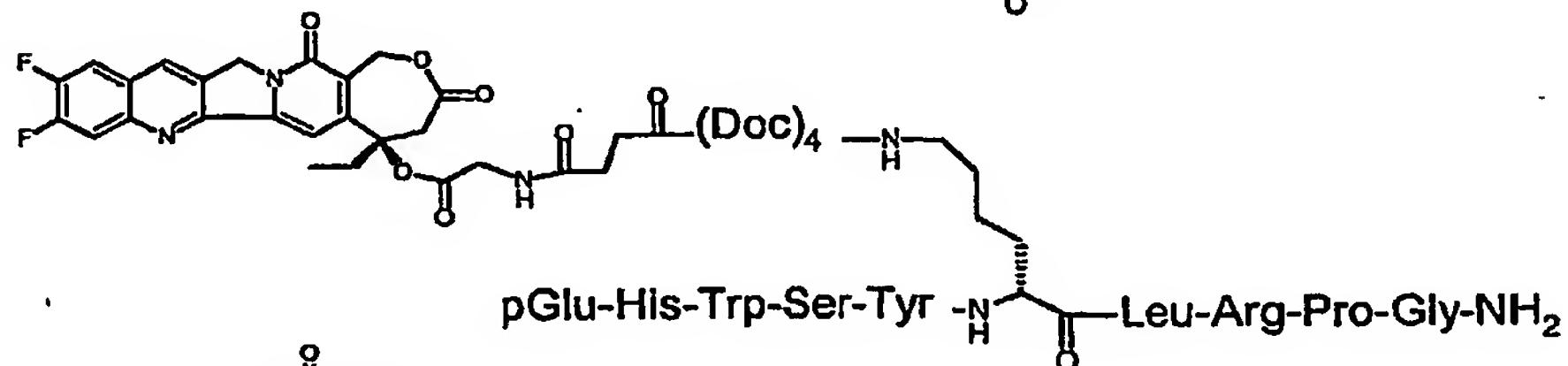
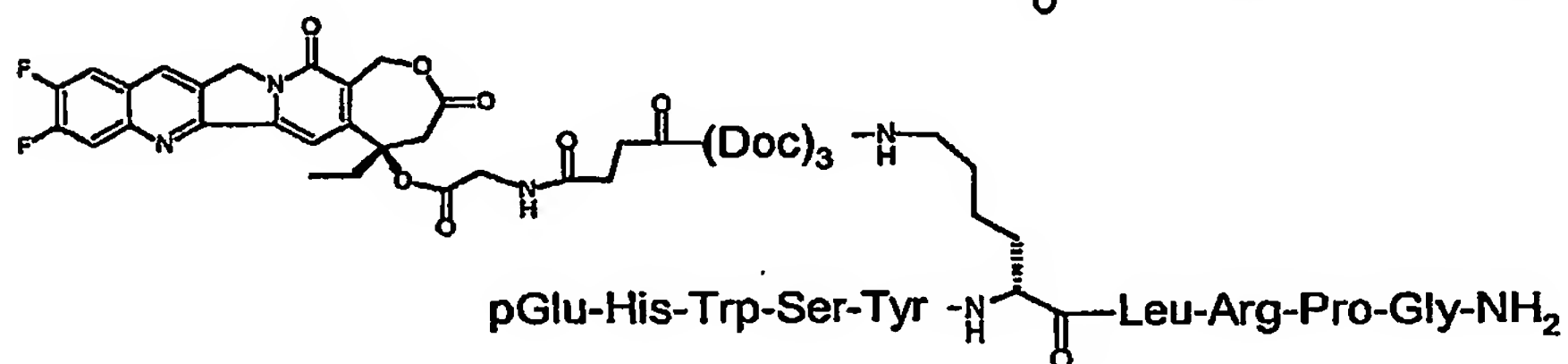
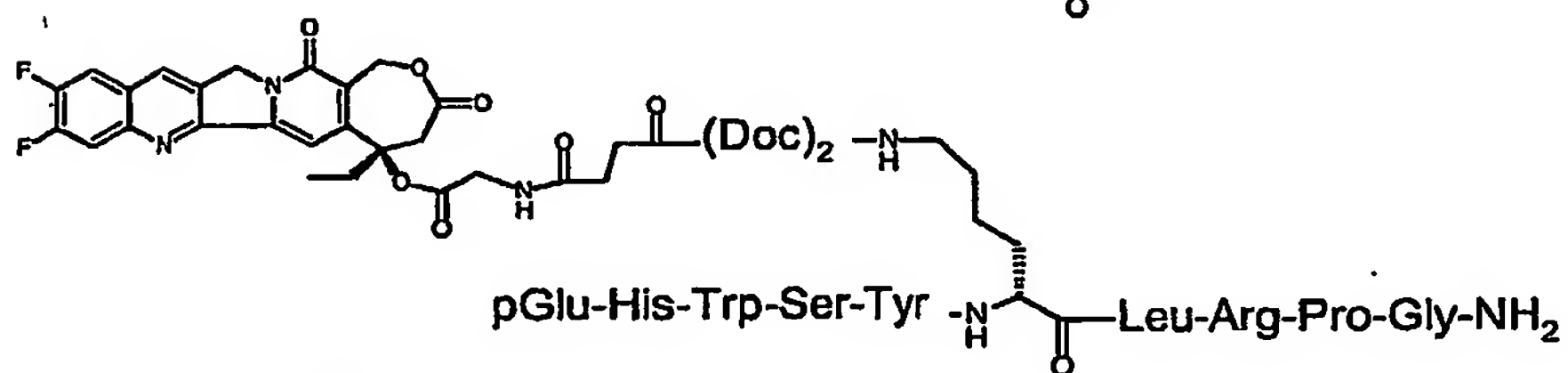
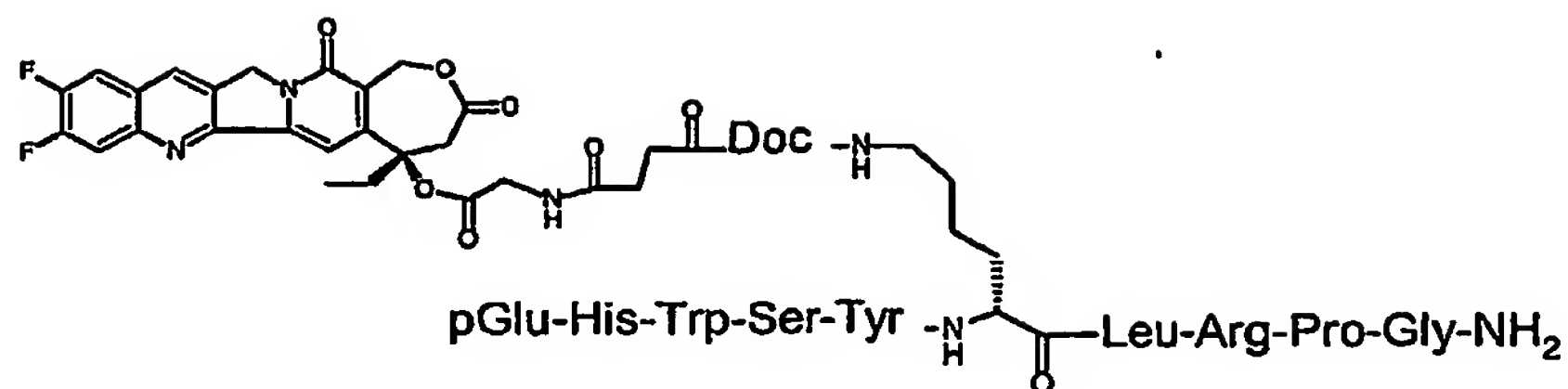


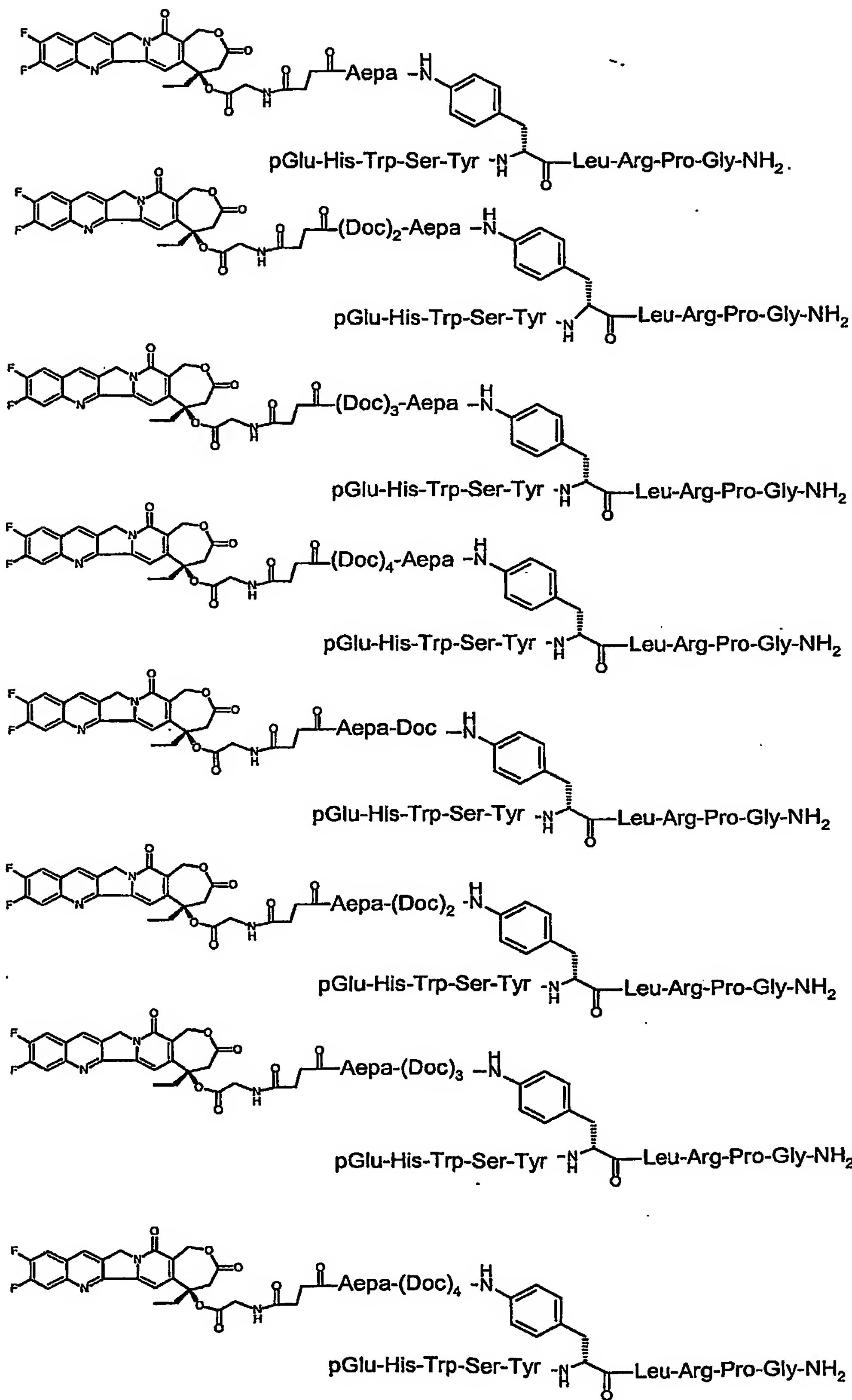






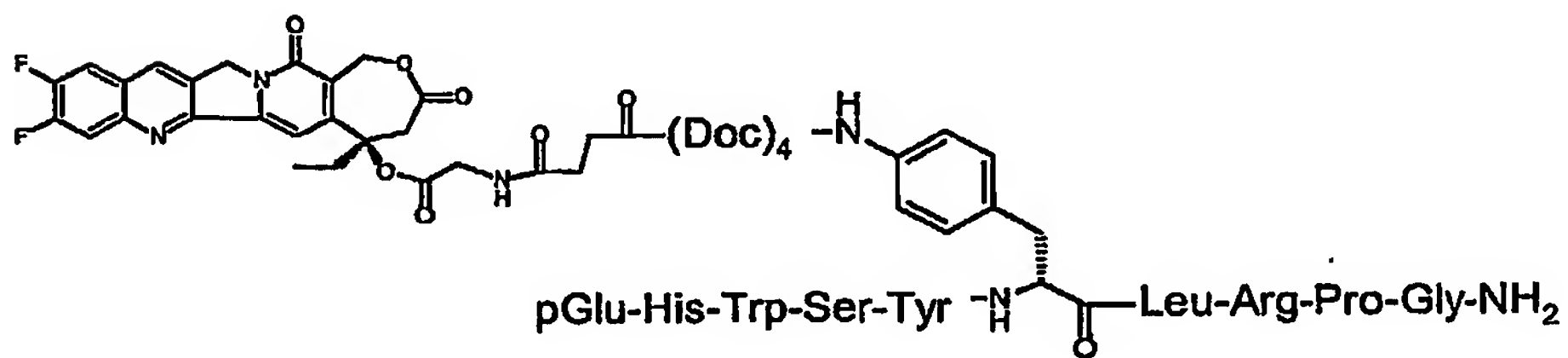
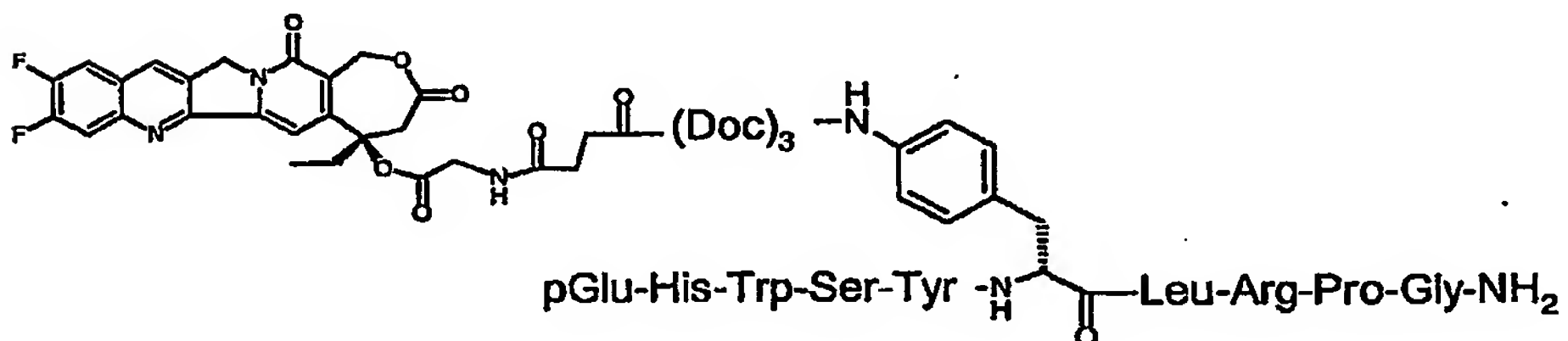
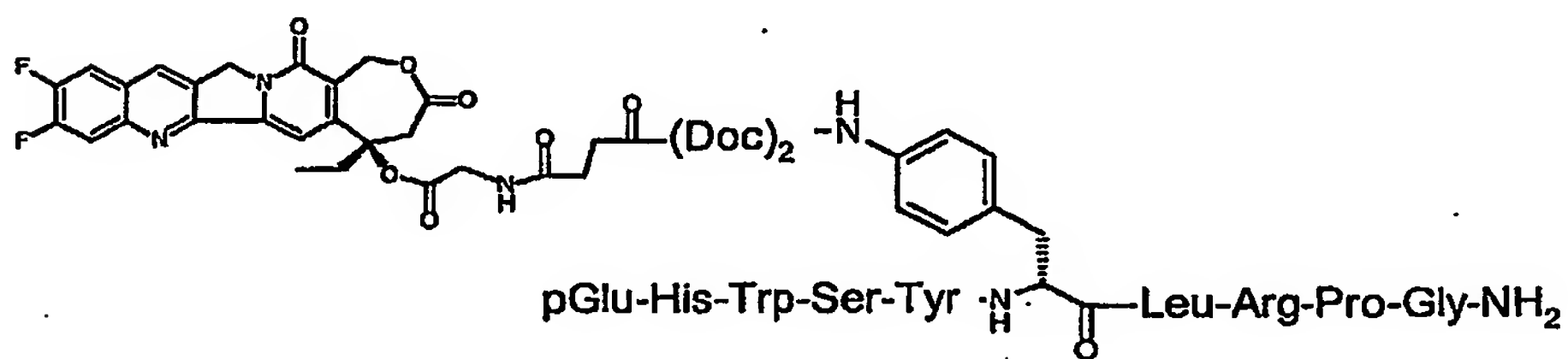
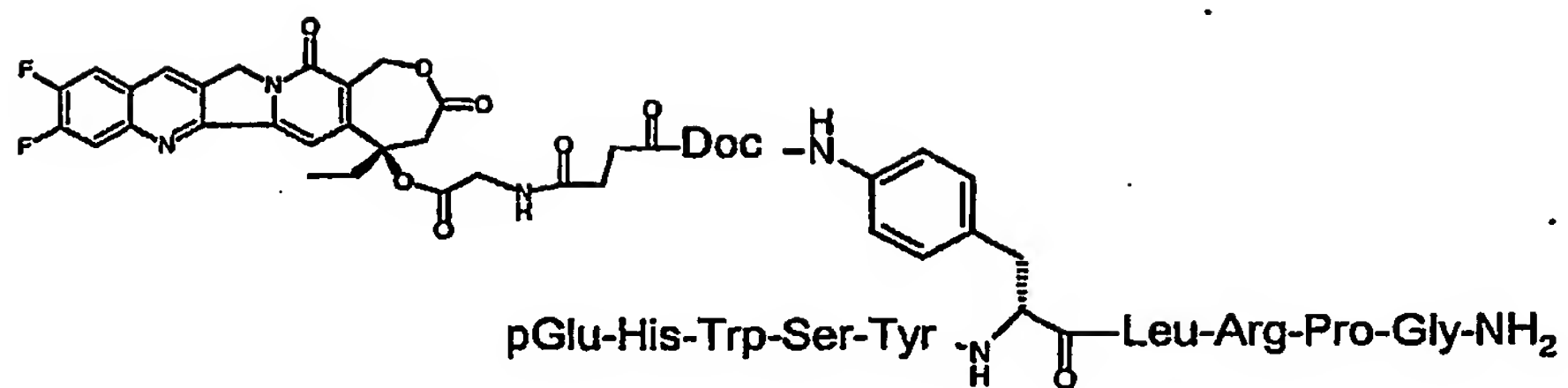


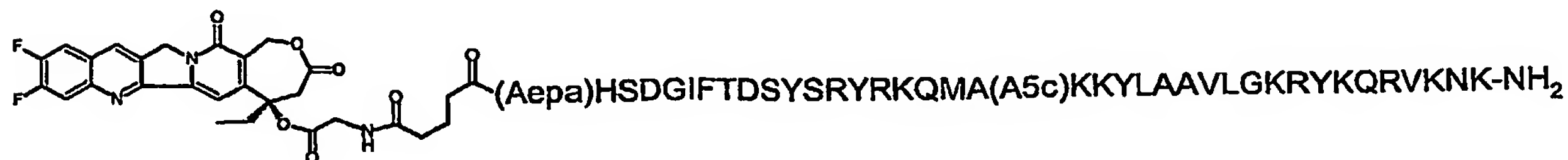
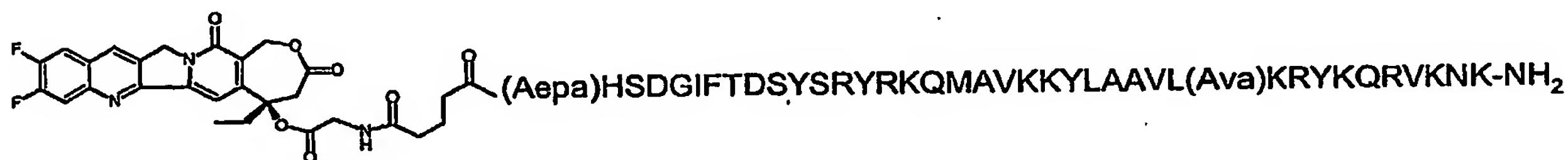
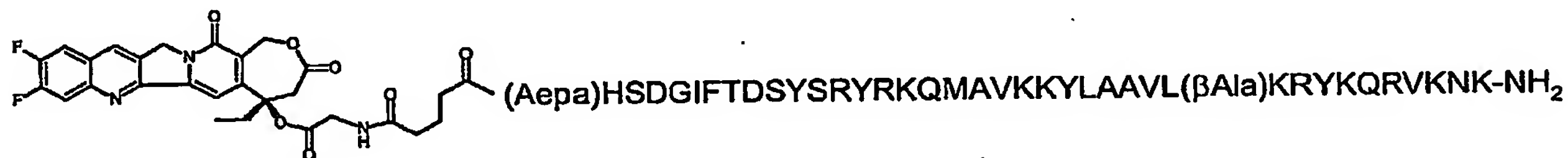
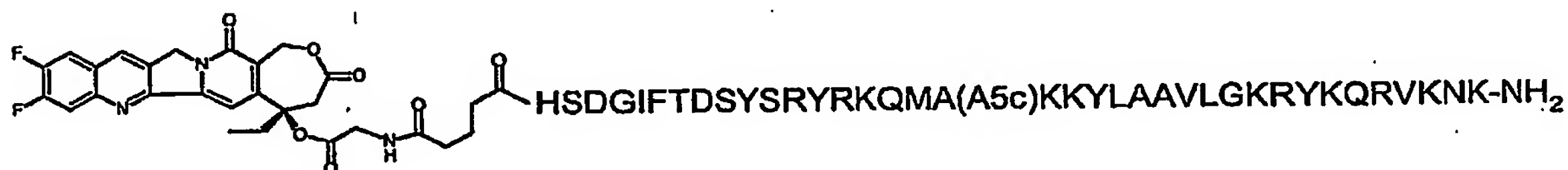


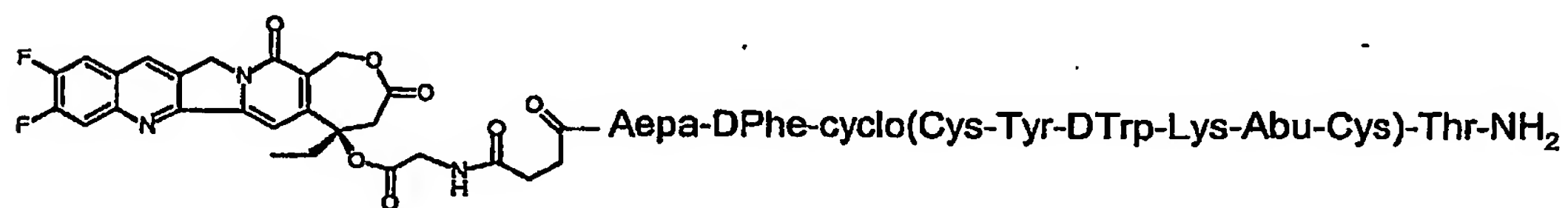
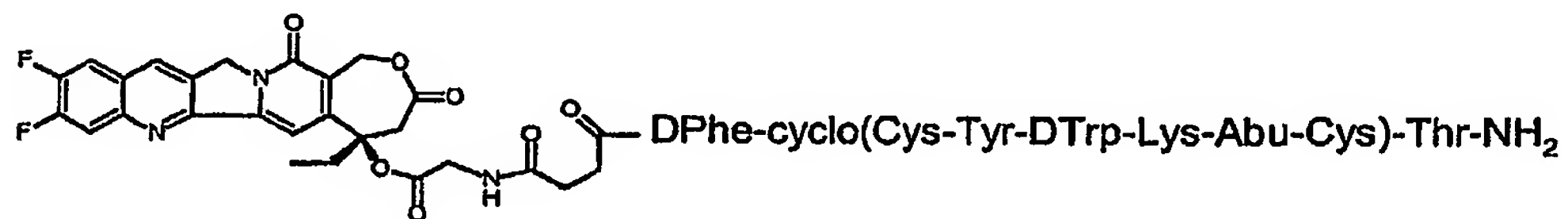
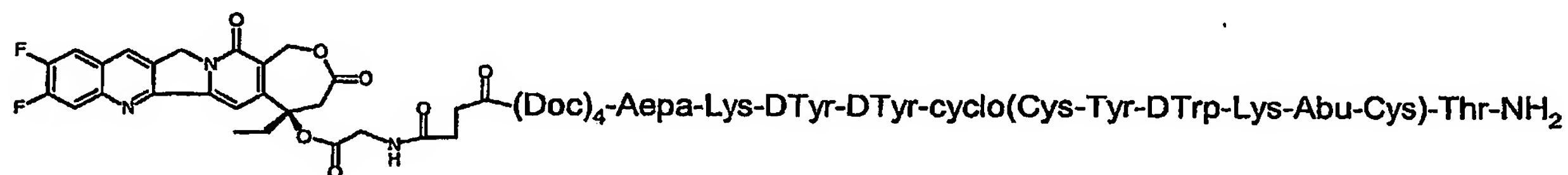
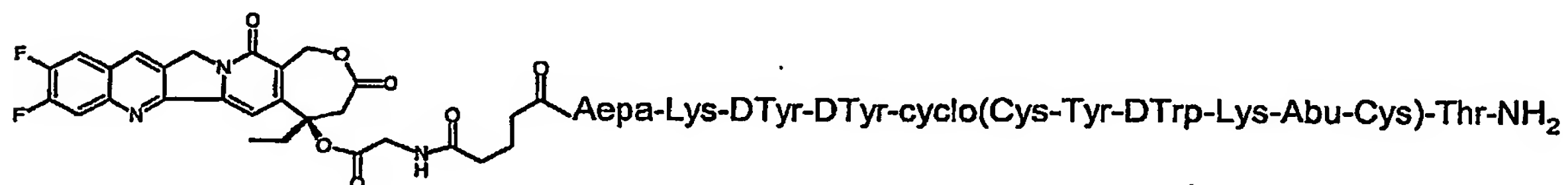
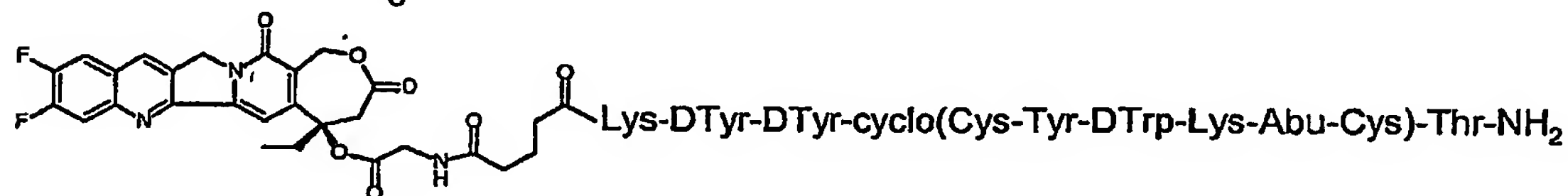
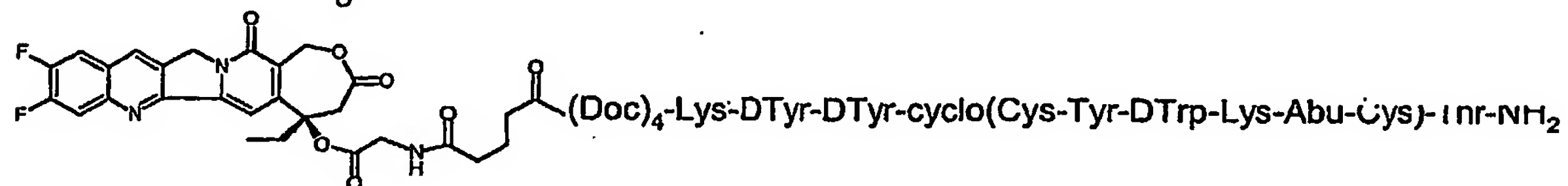
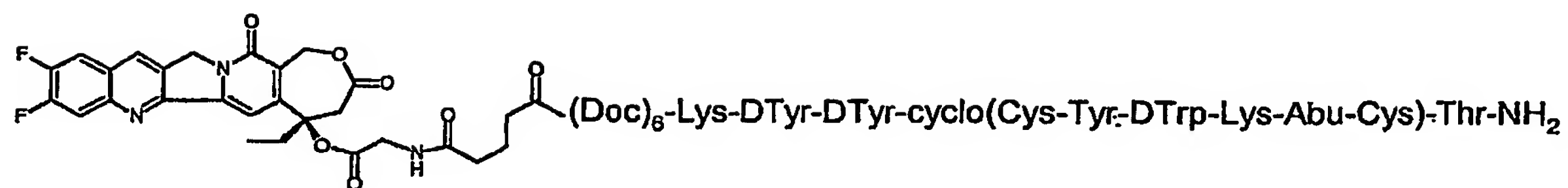


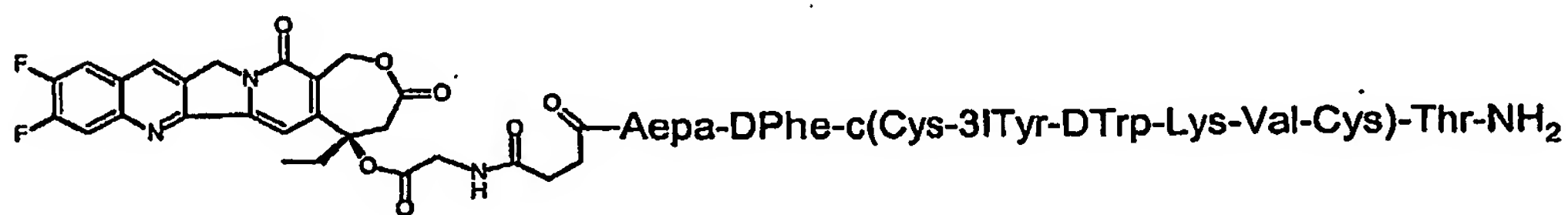
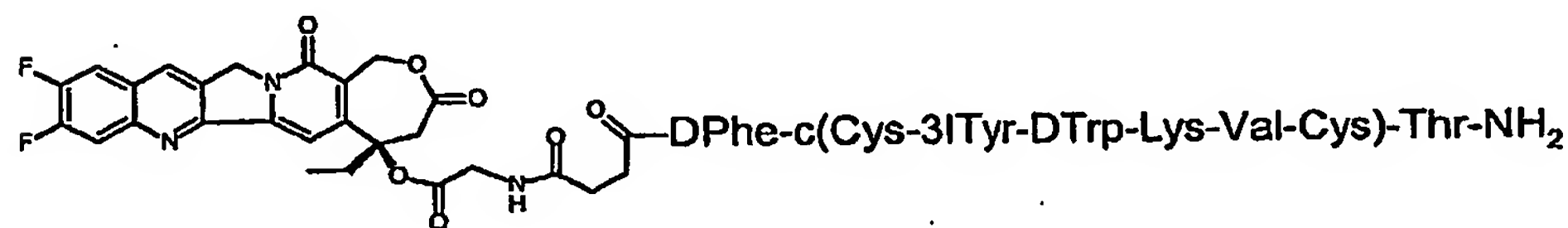
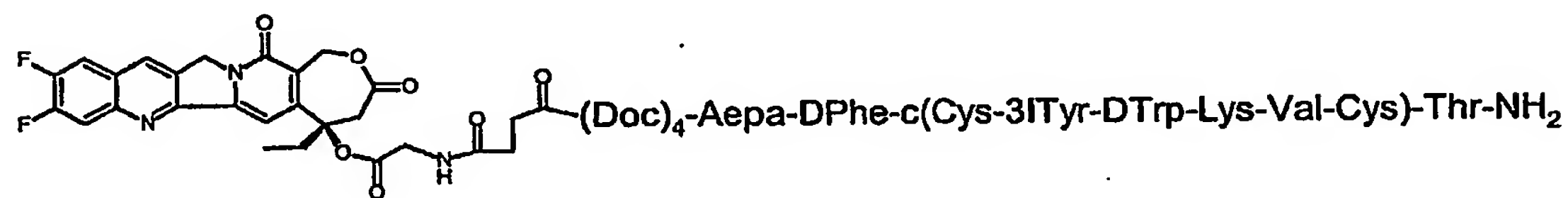
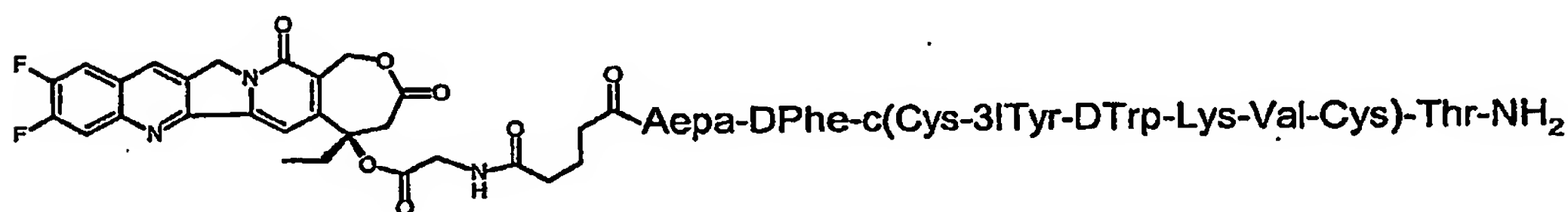
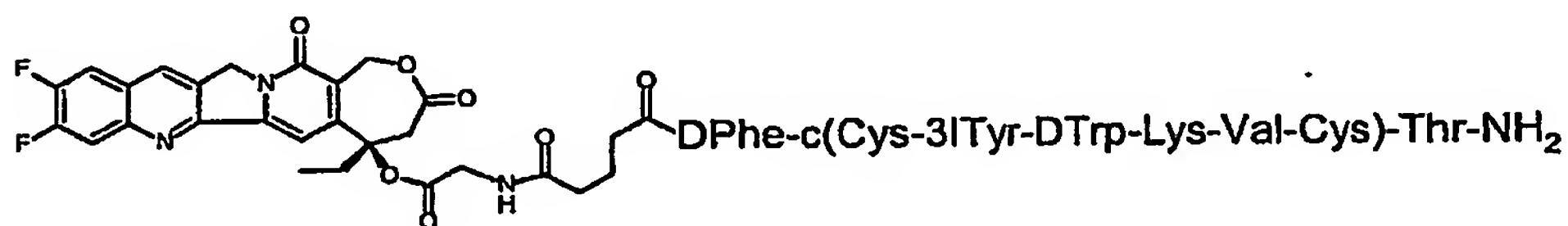
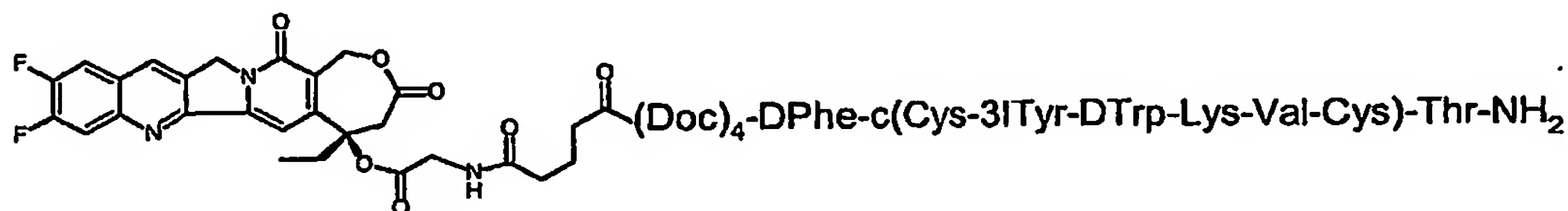
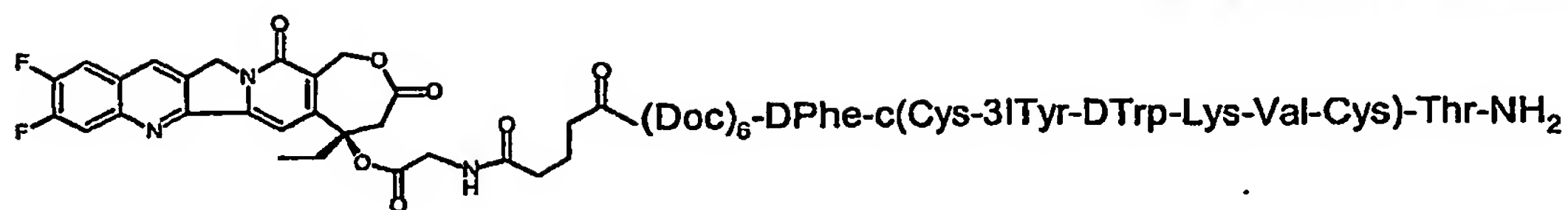
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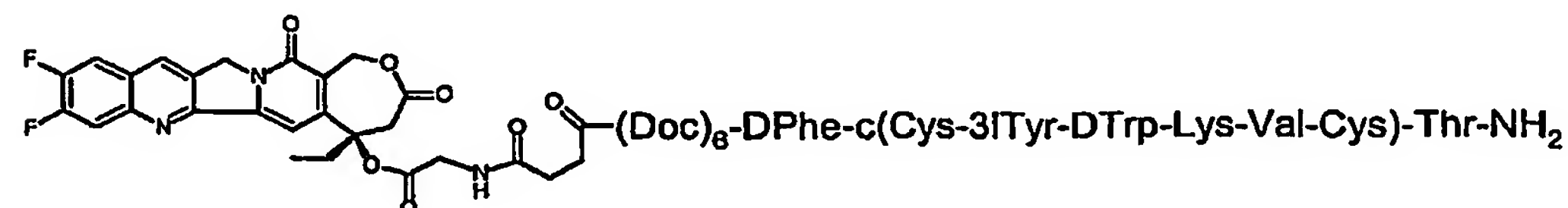
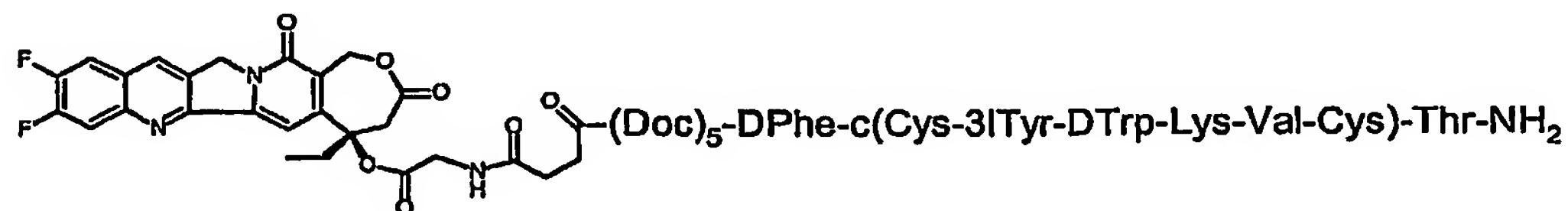
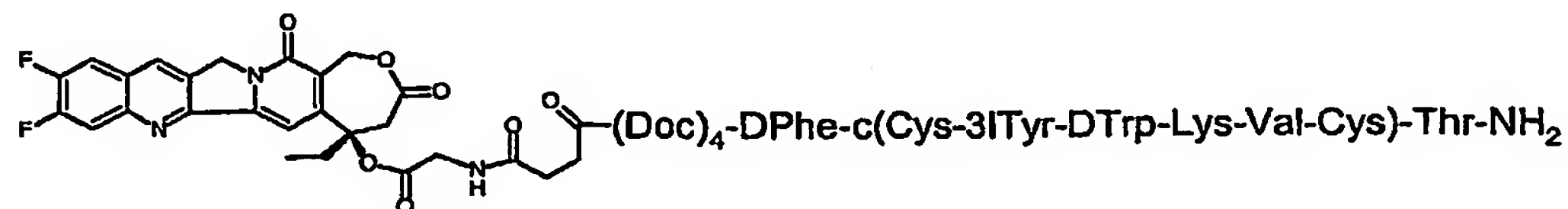
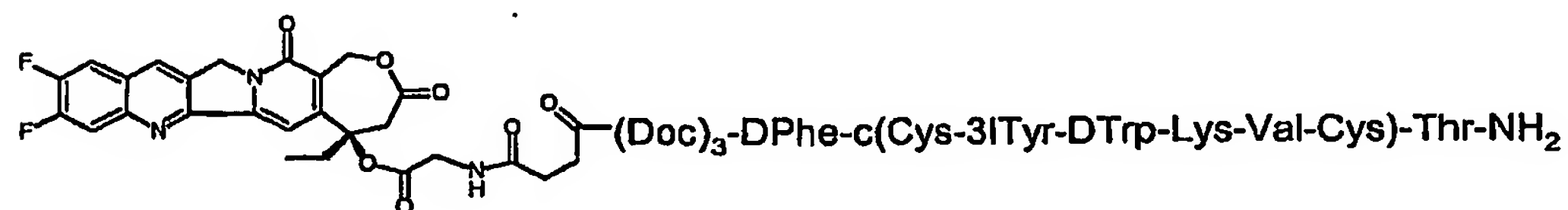
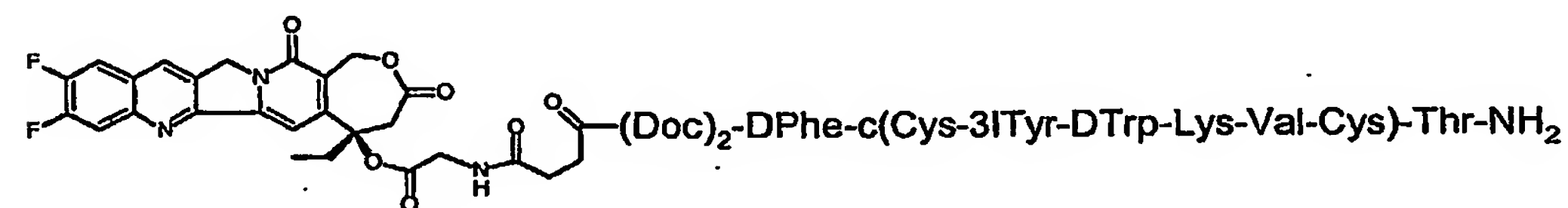
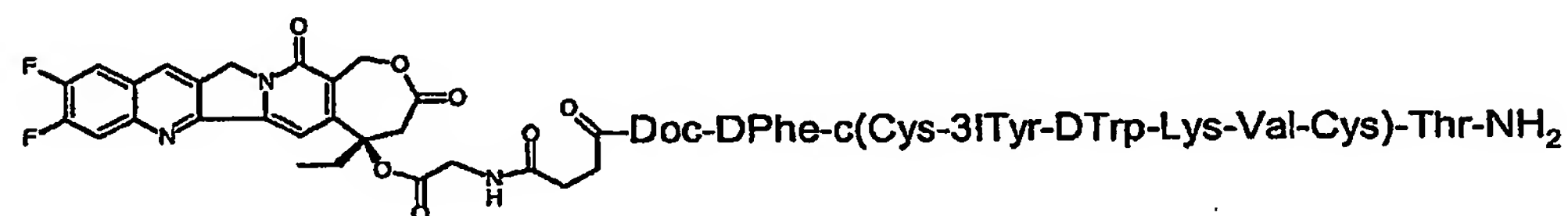
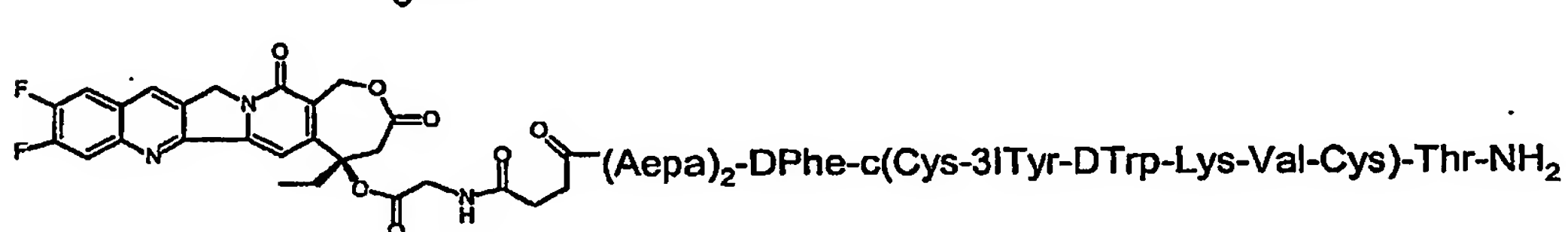
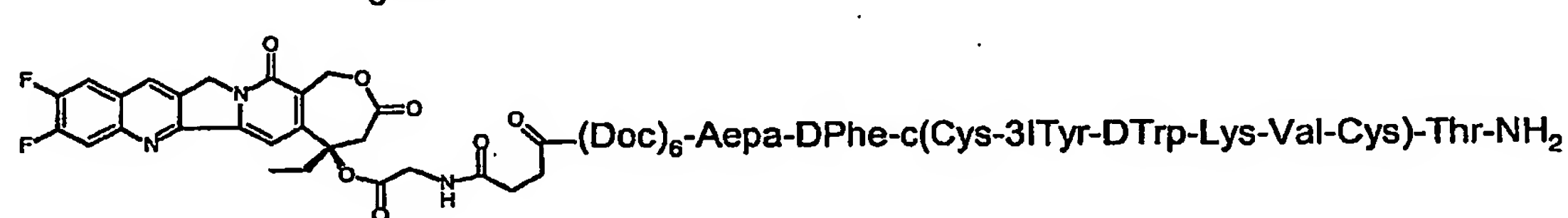
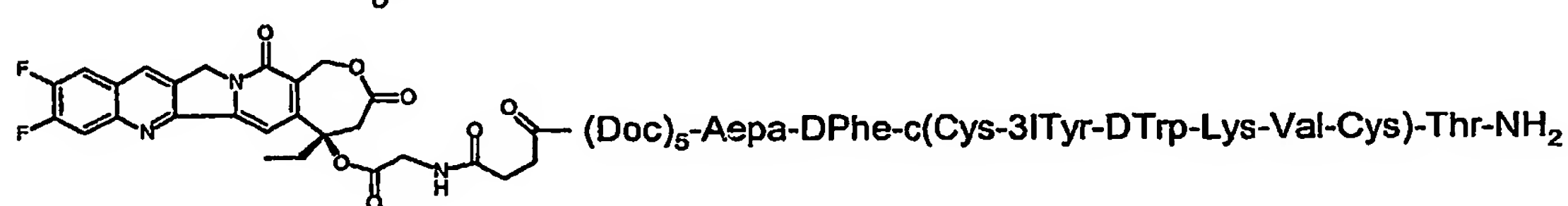
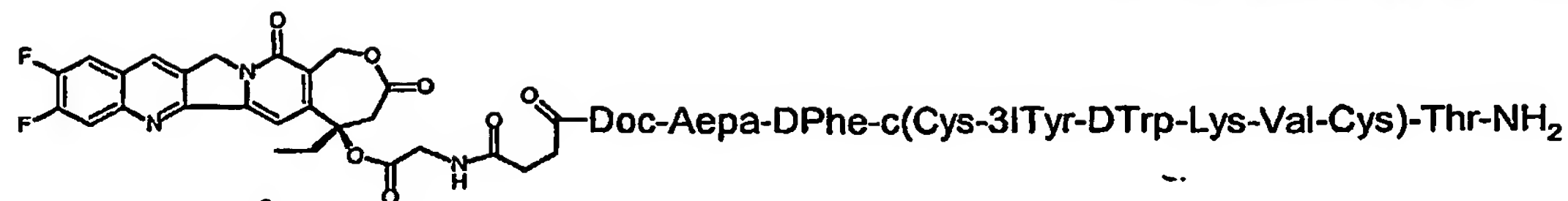
Appendix B

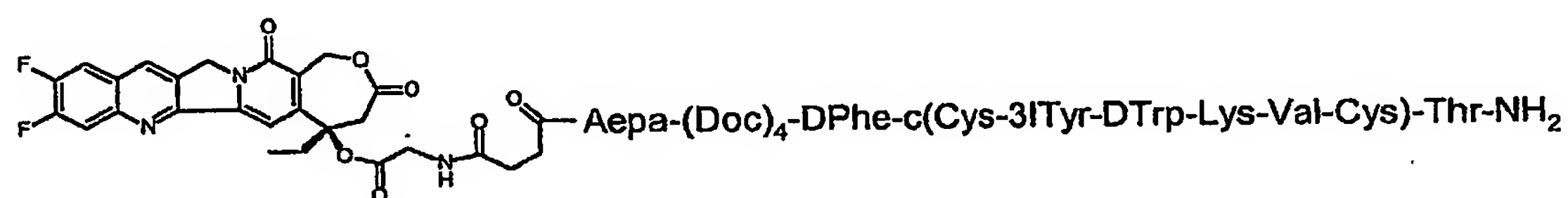
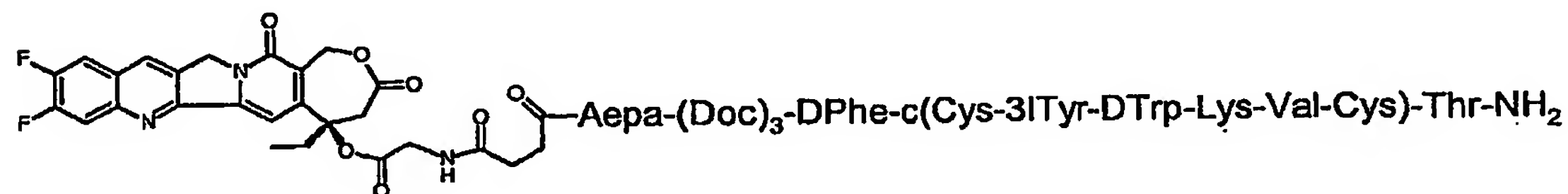
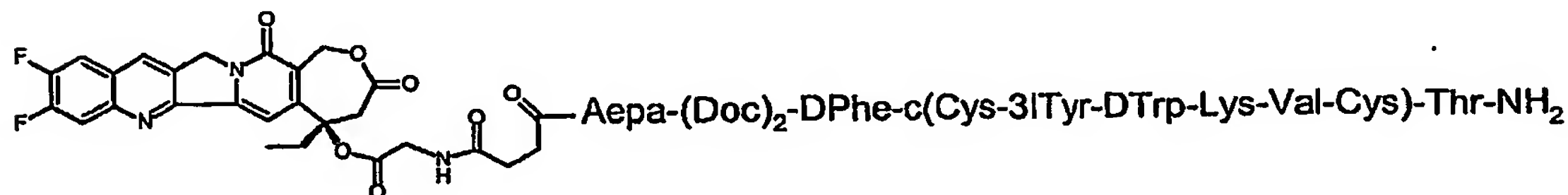
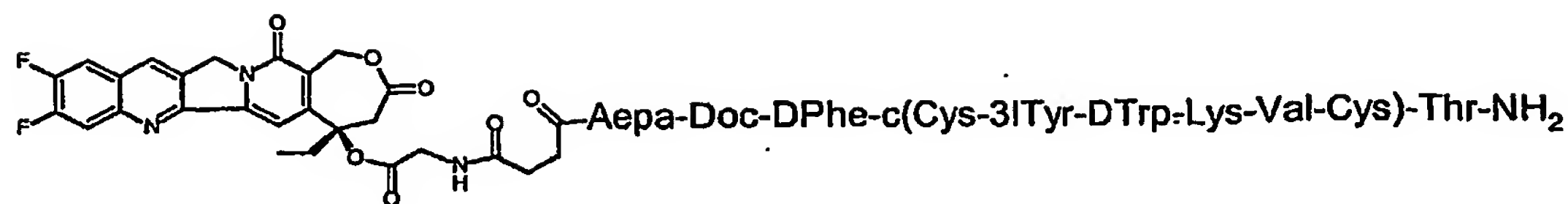


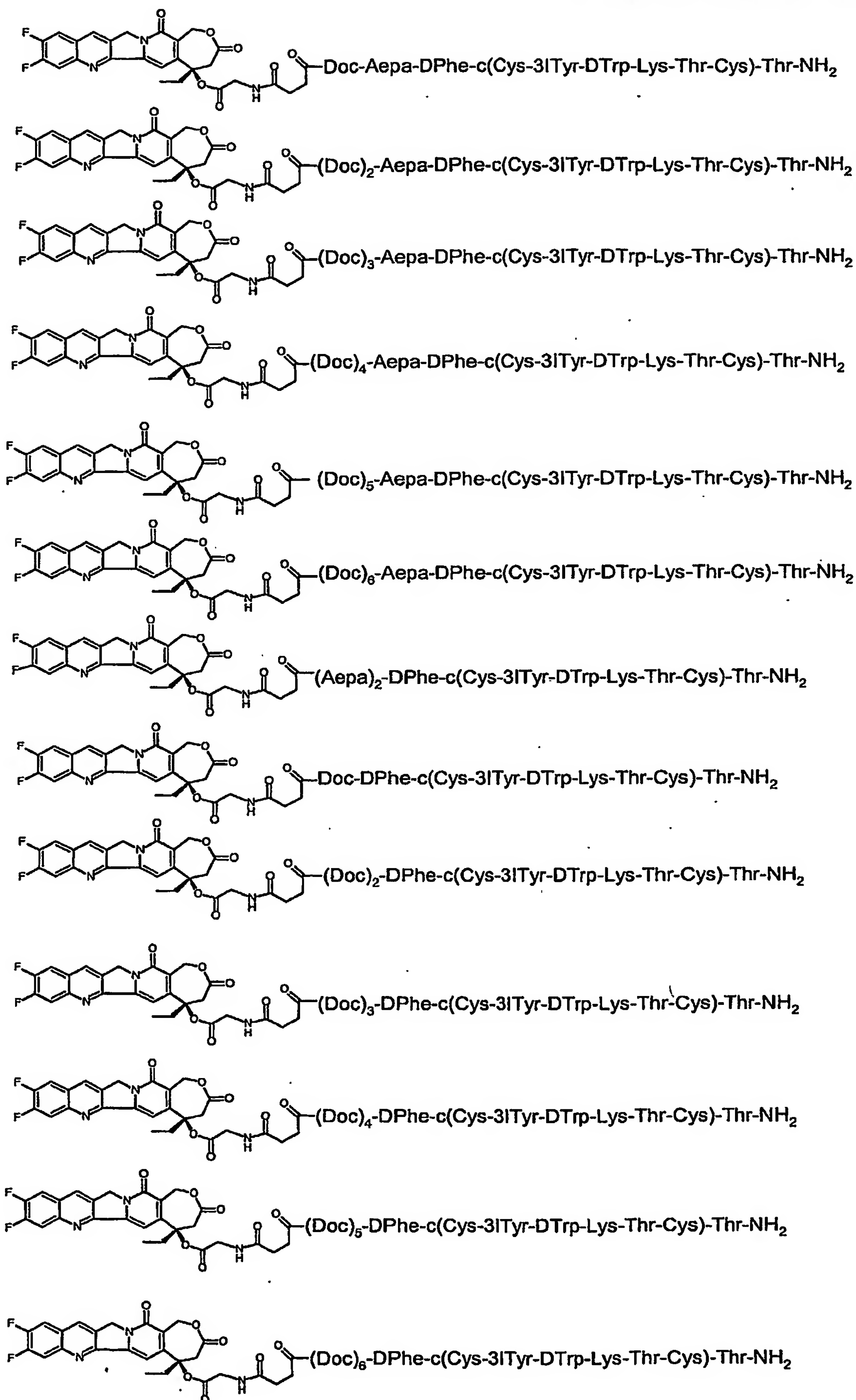


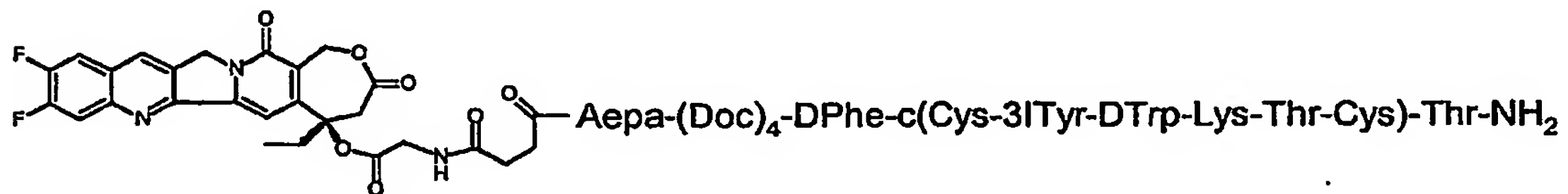
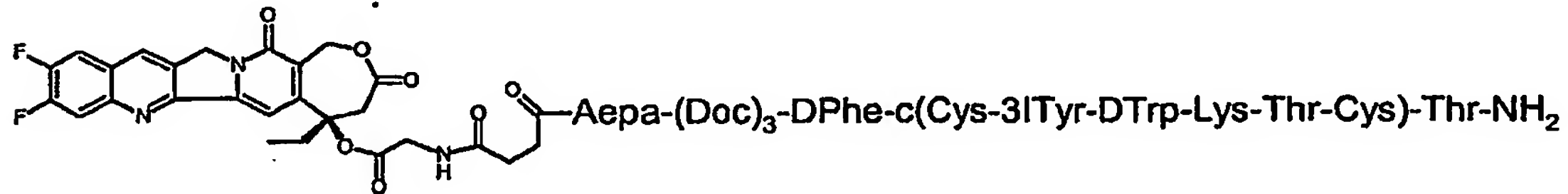
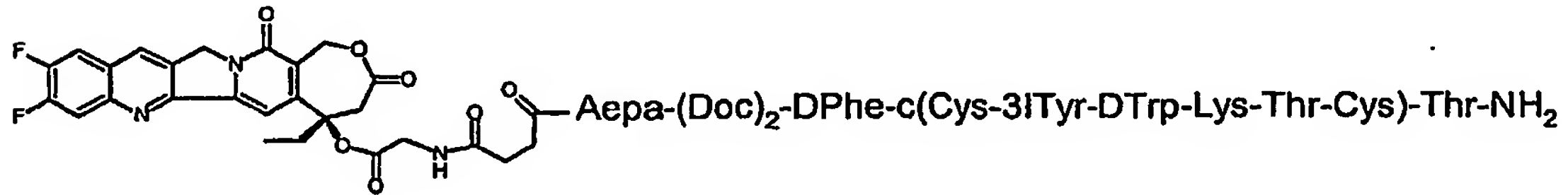
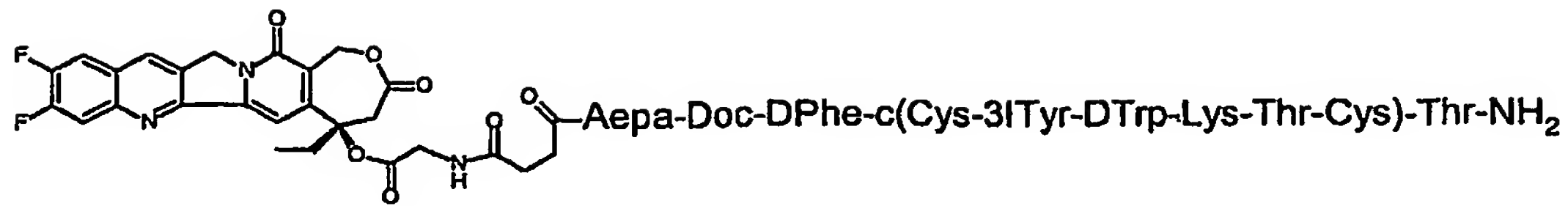


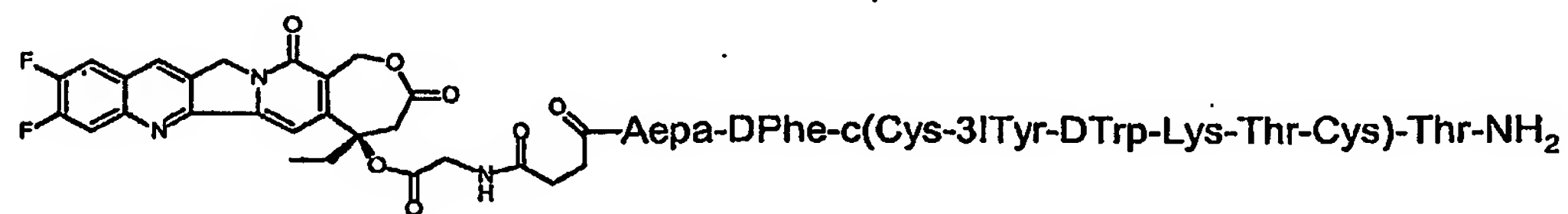
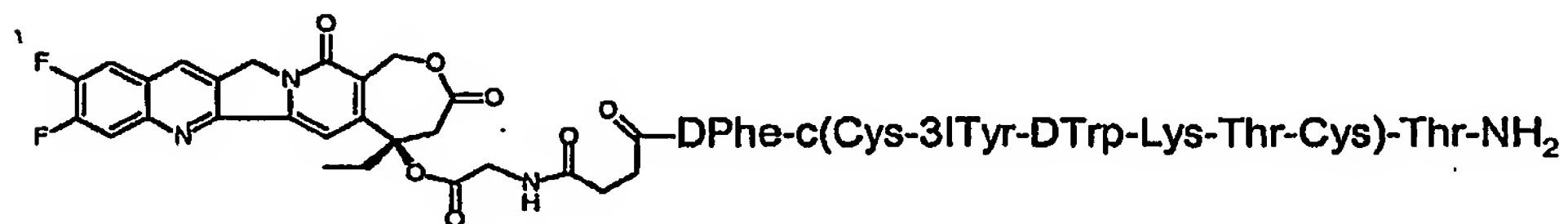
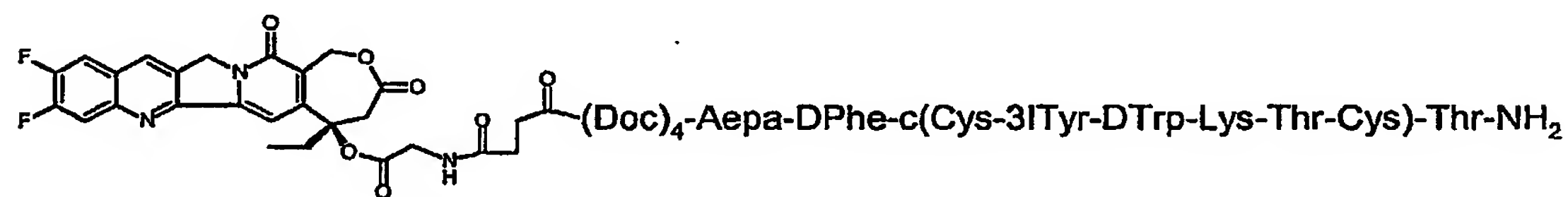
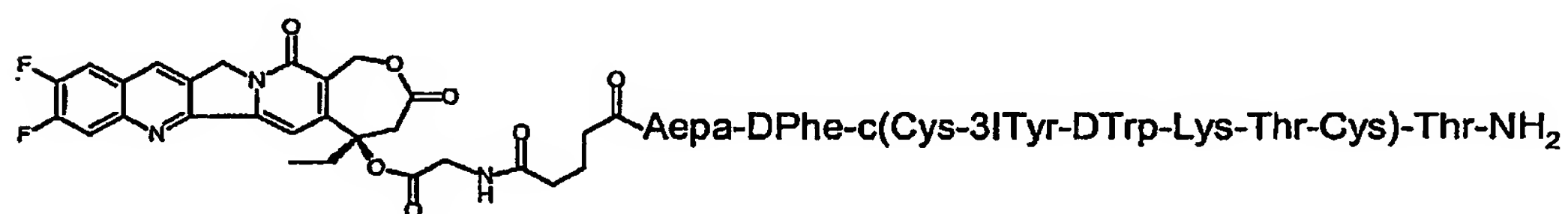
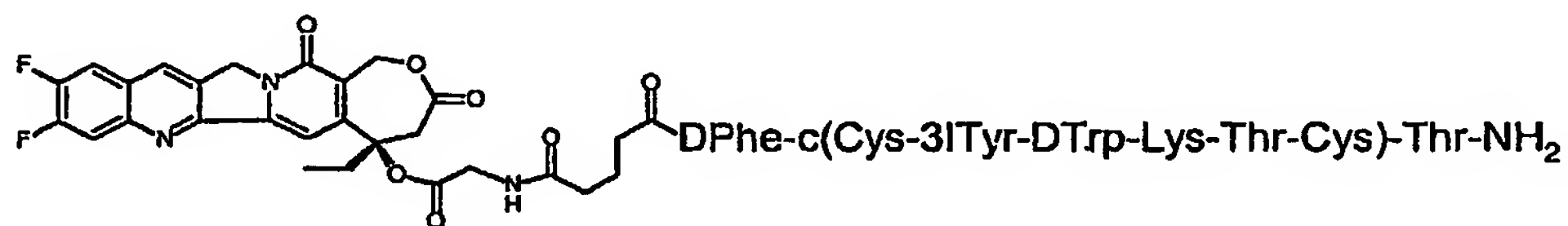
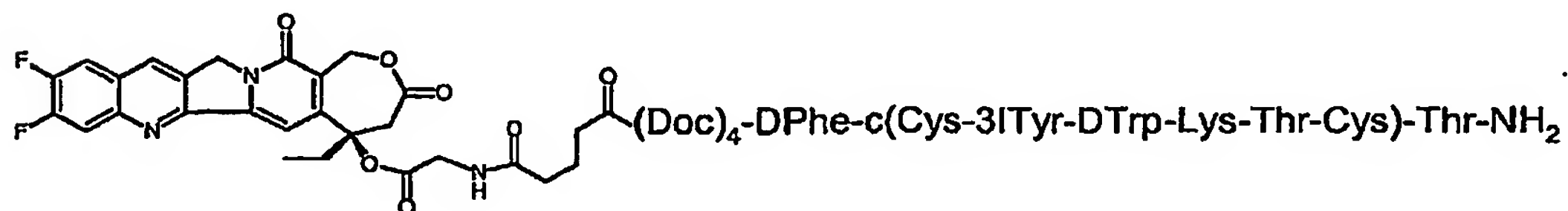
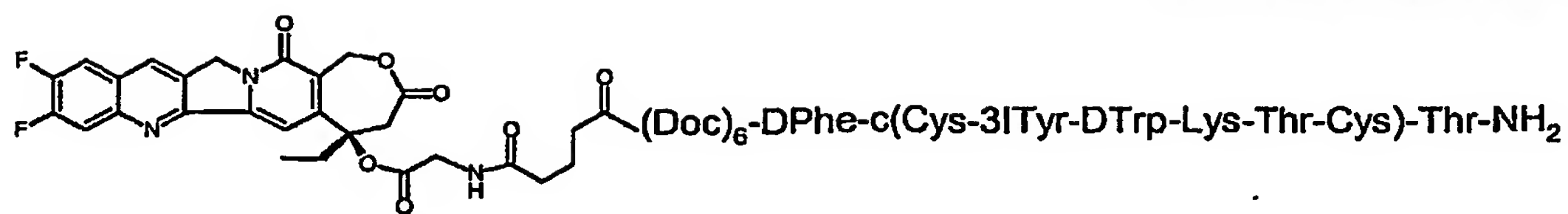


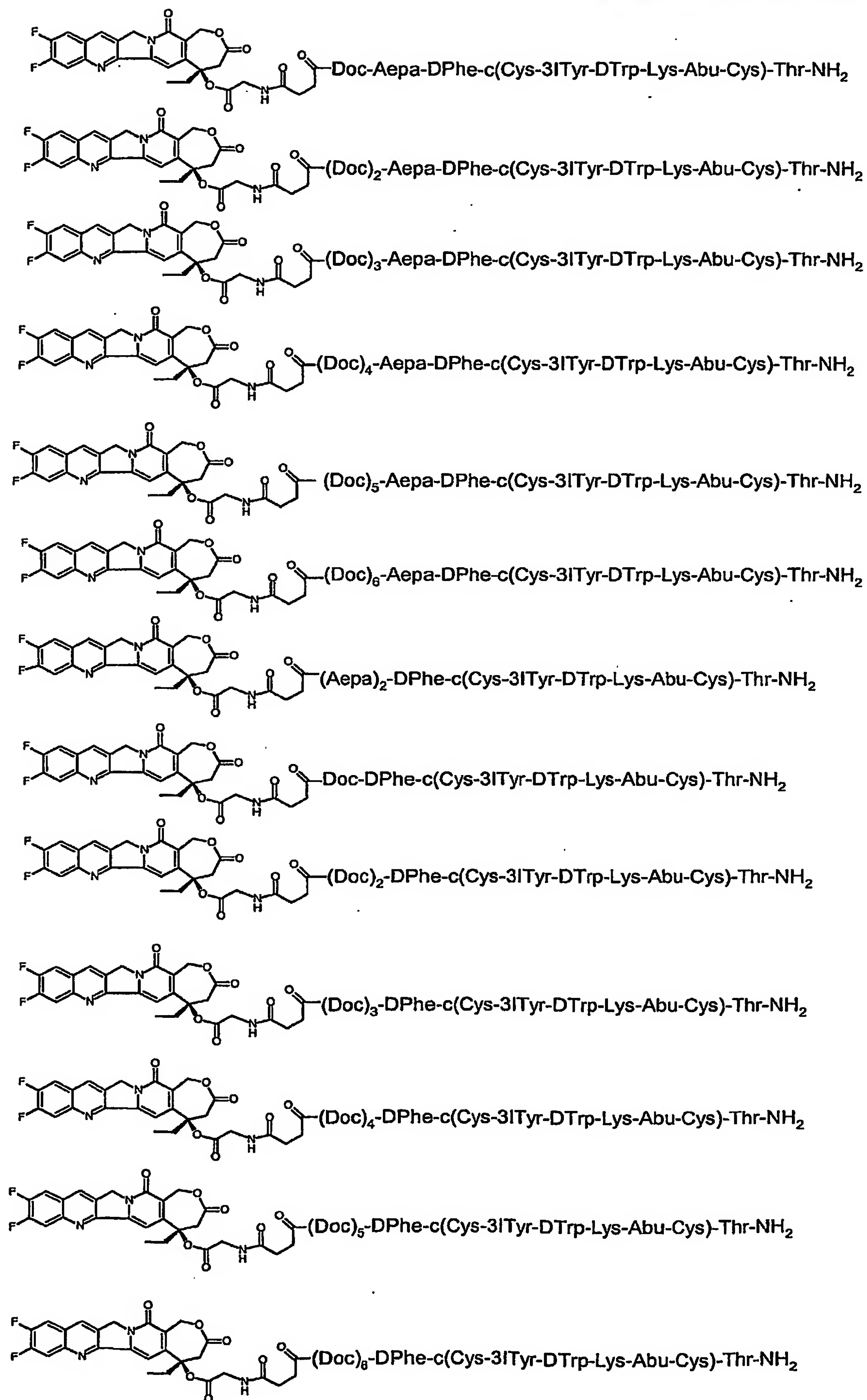


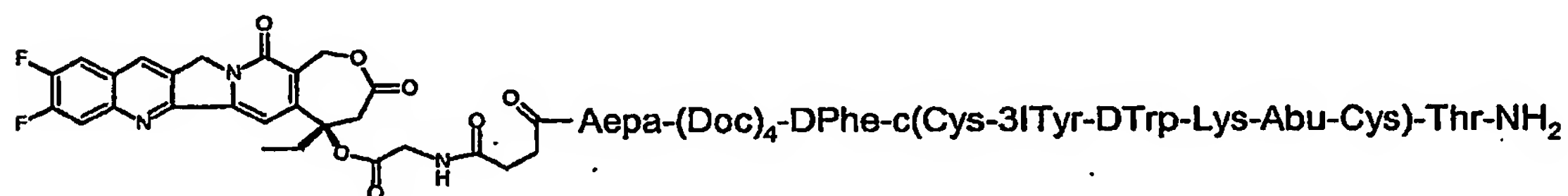
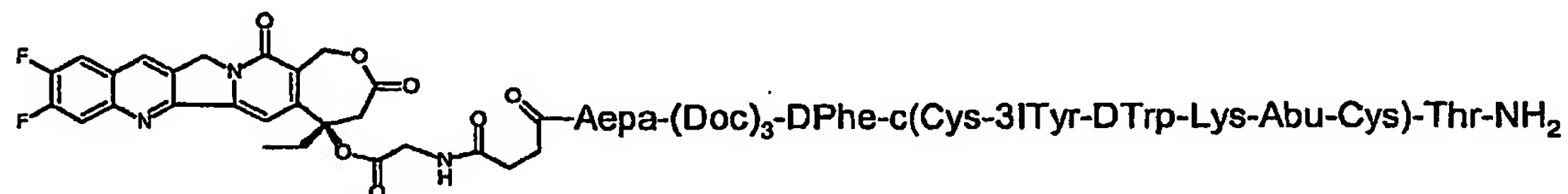
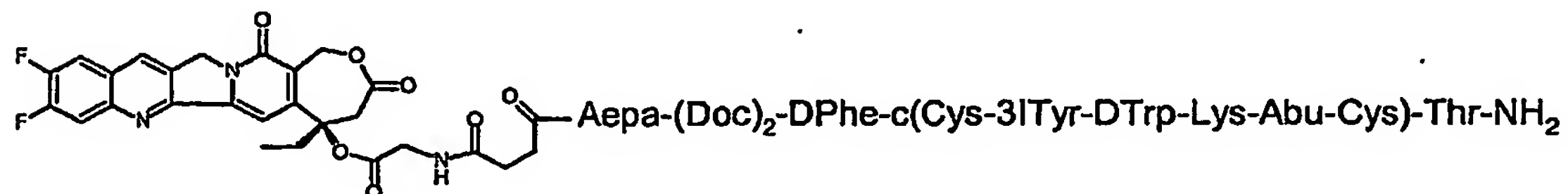
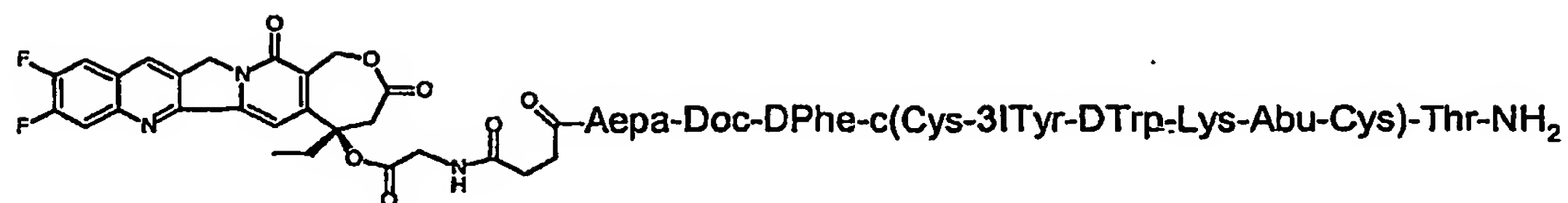


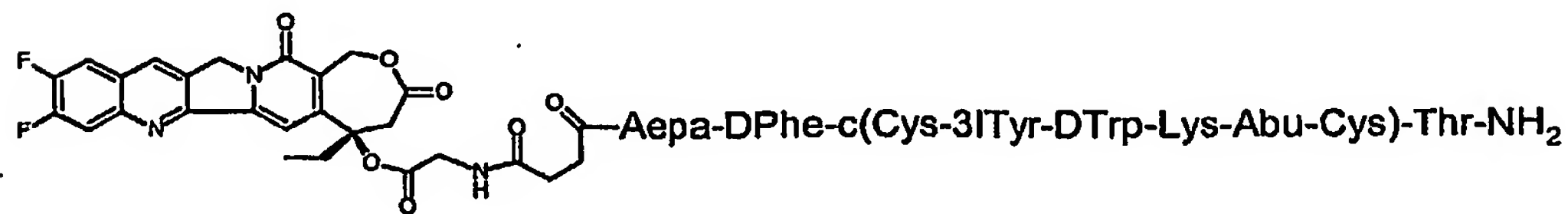
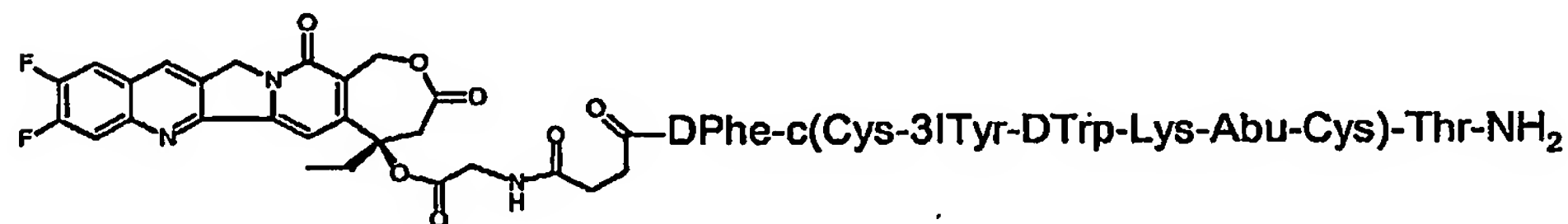
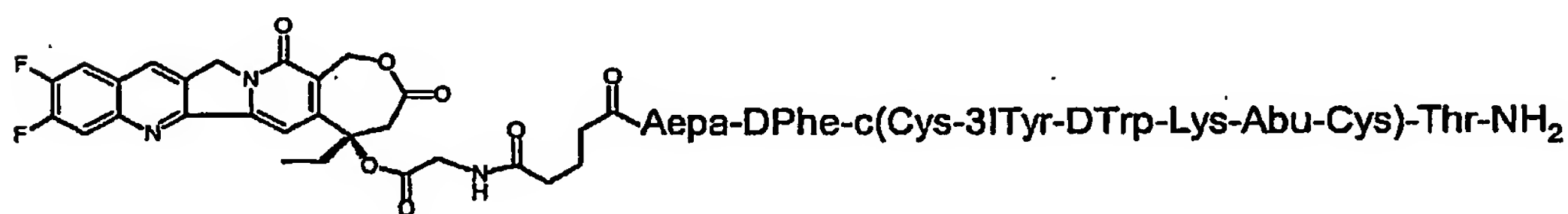
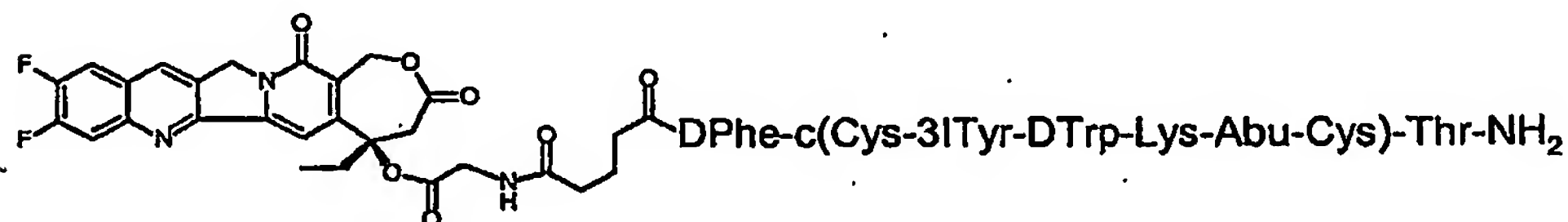
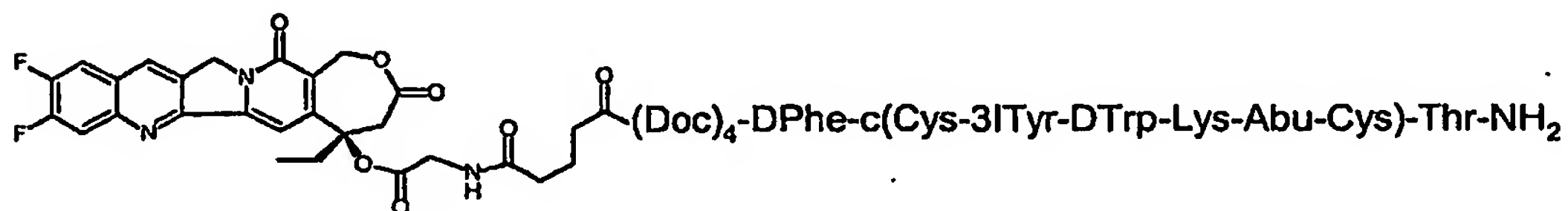
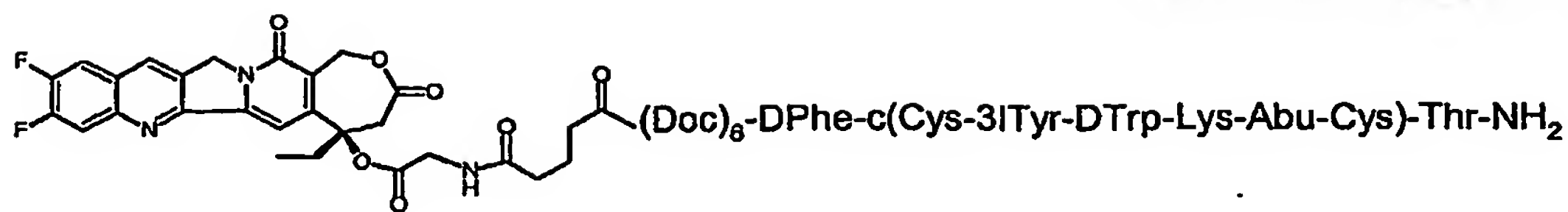


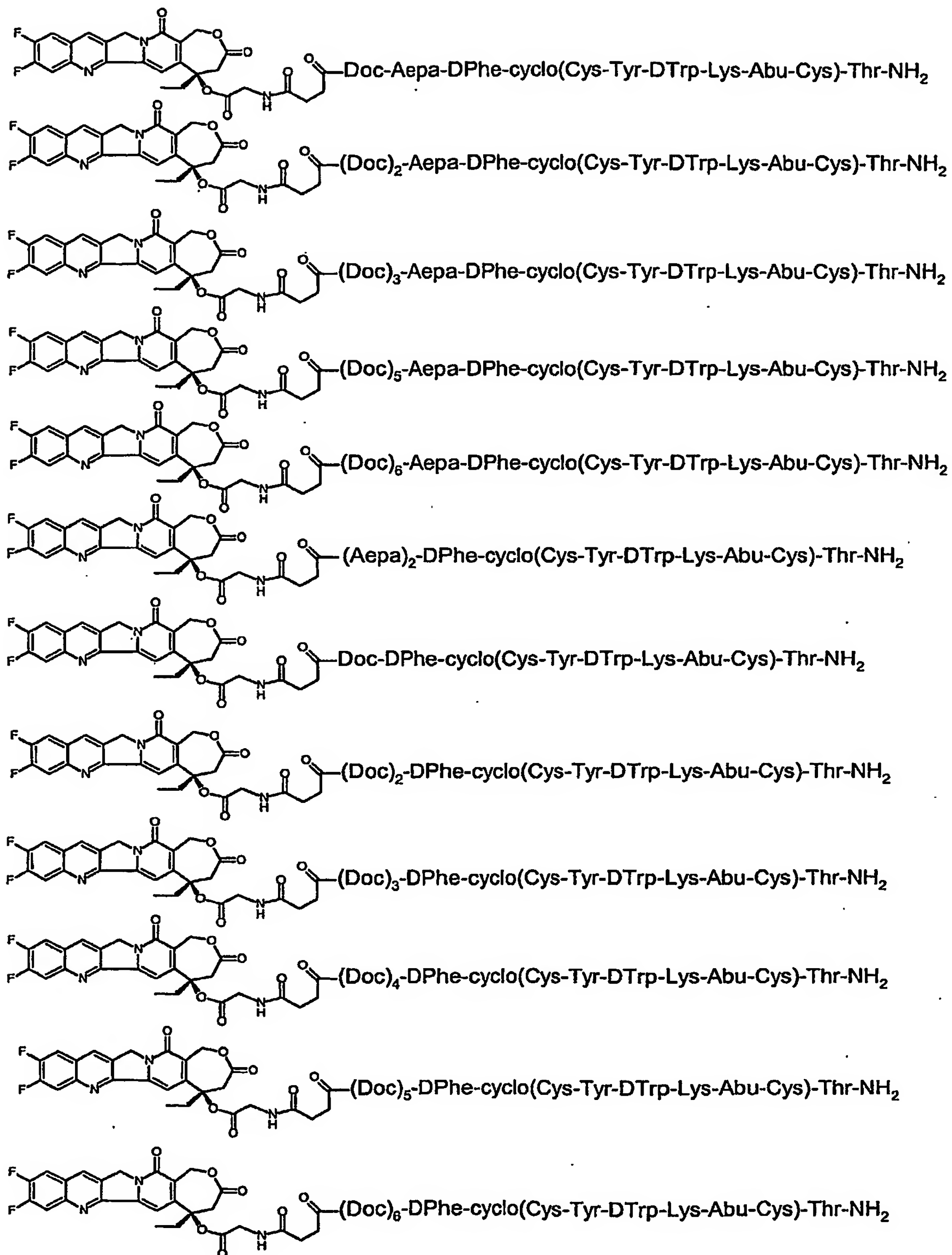


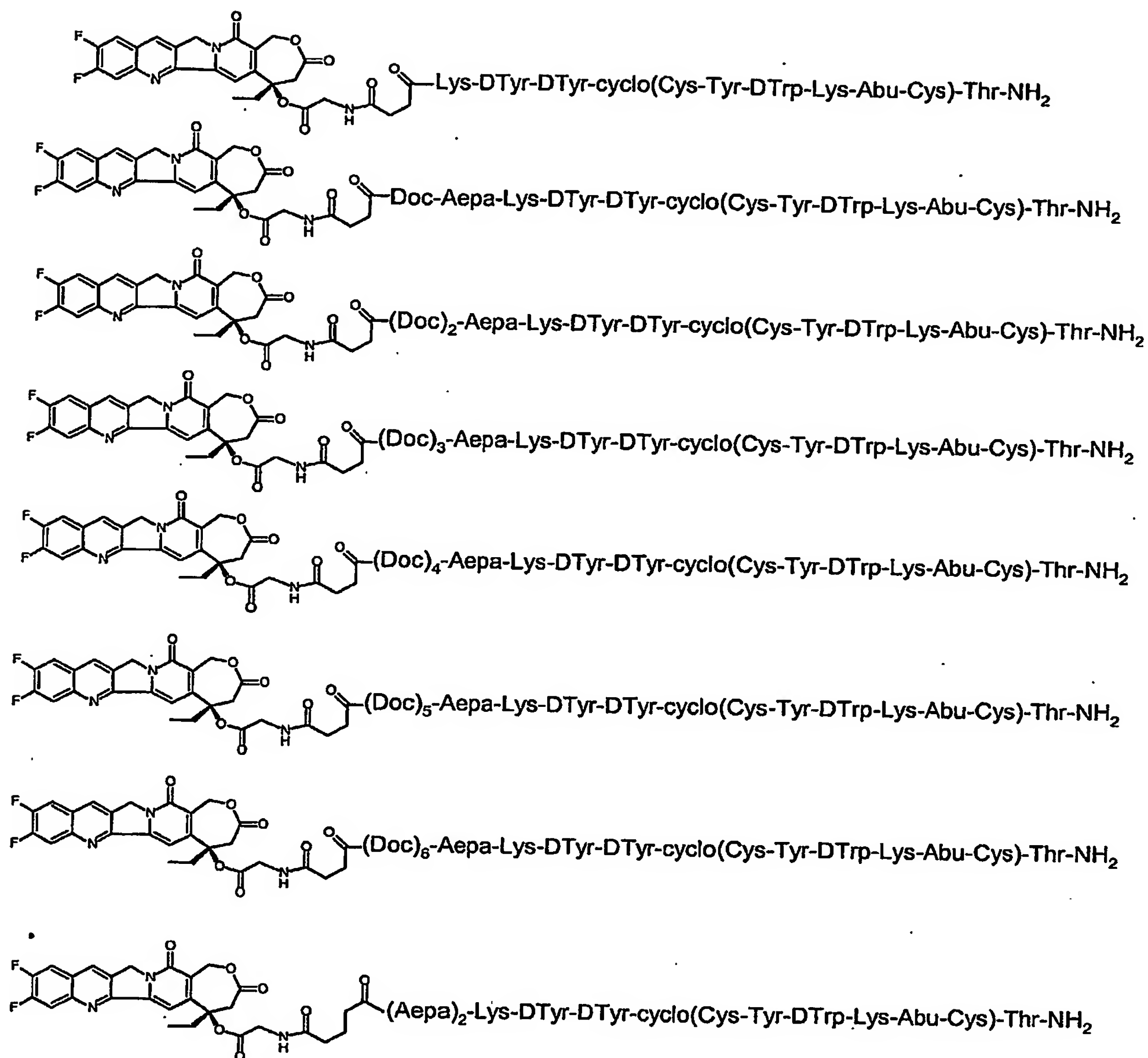


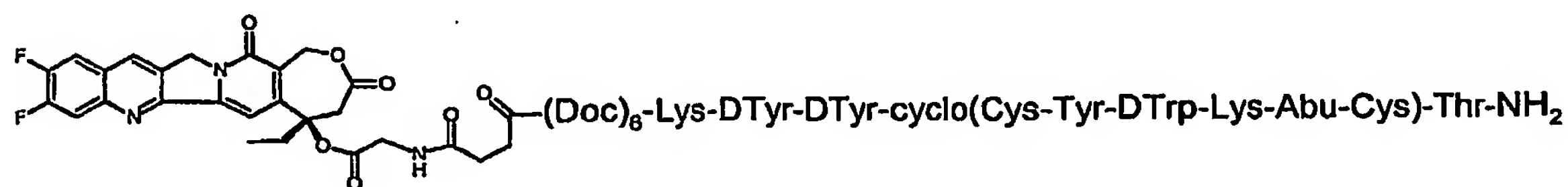
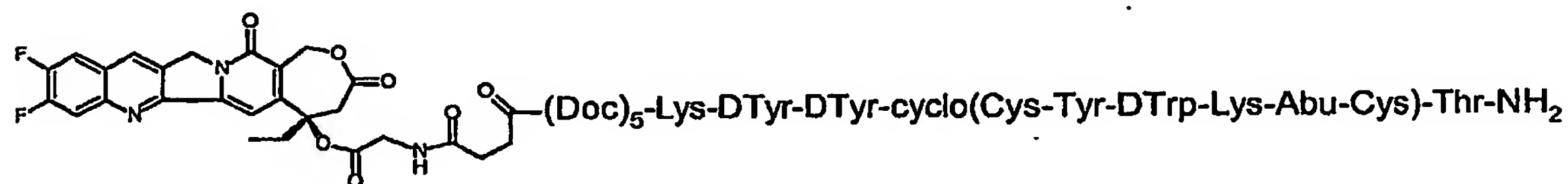
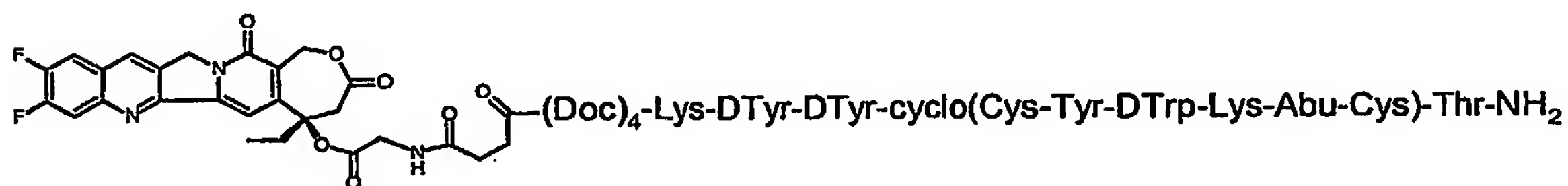
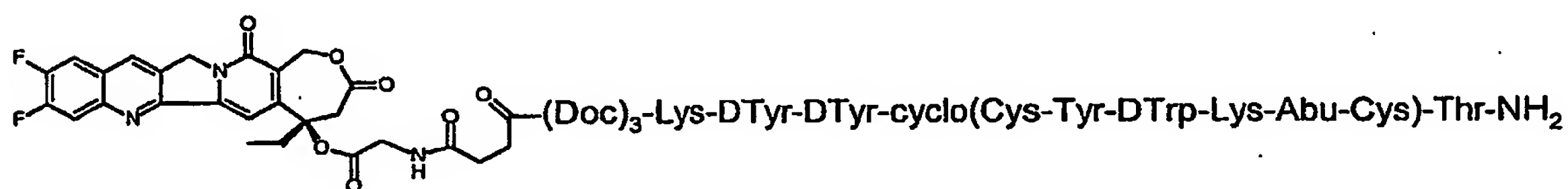
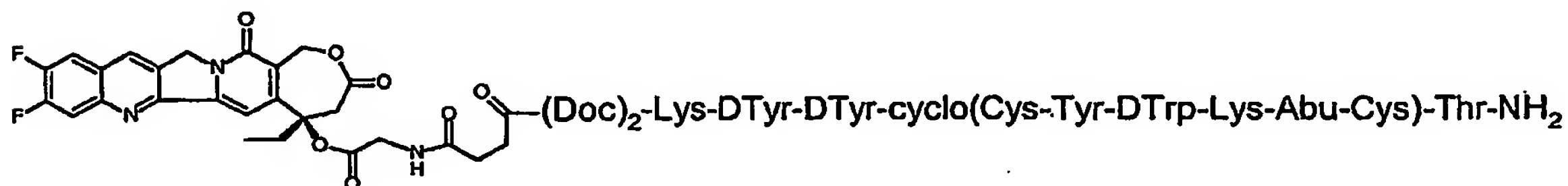
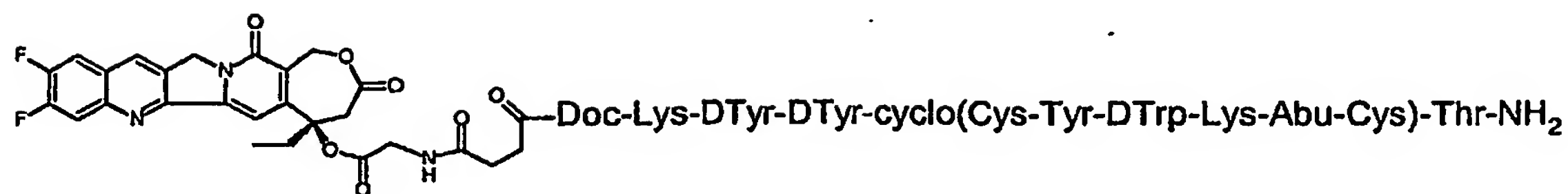


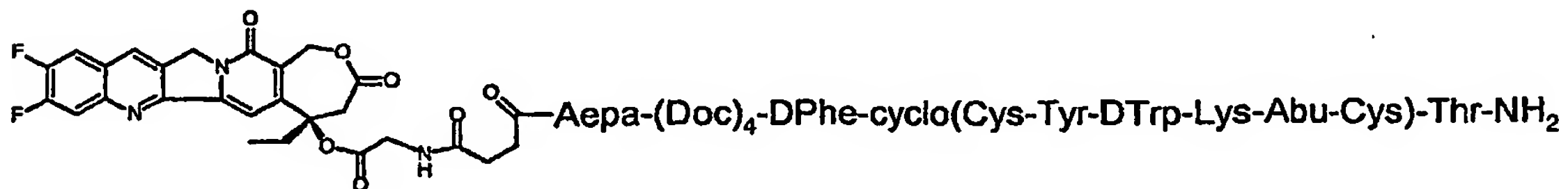
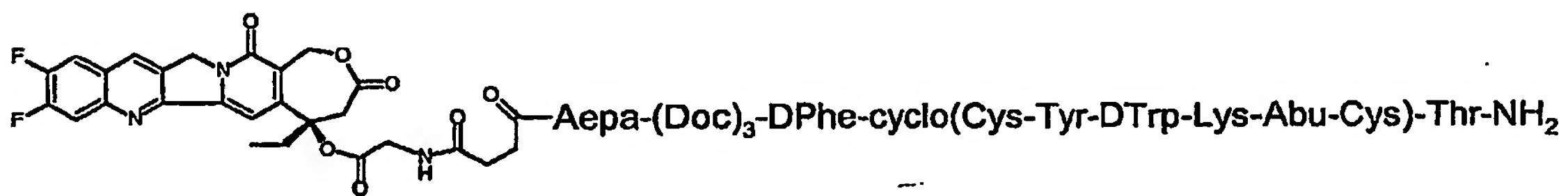
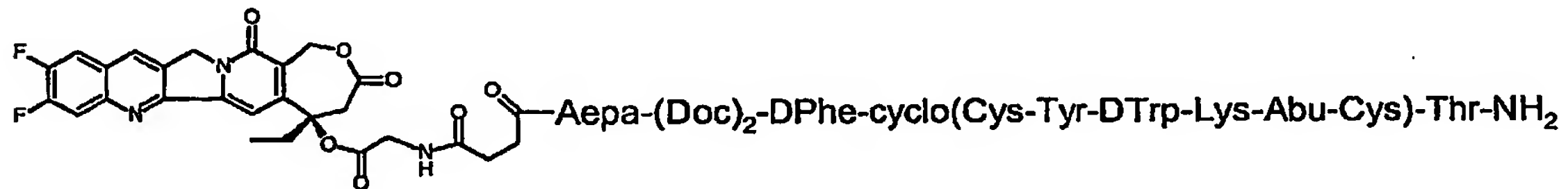
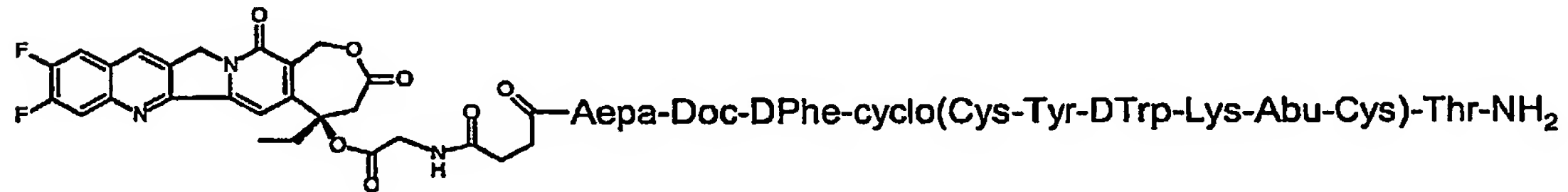
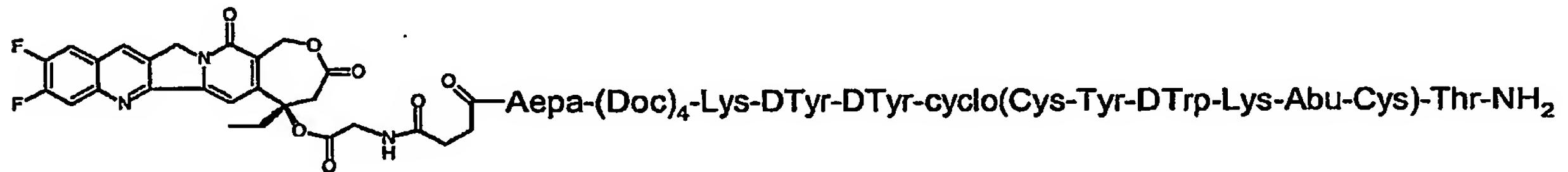
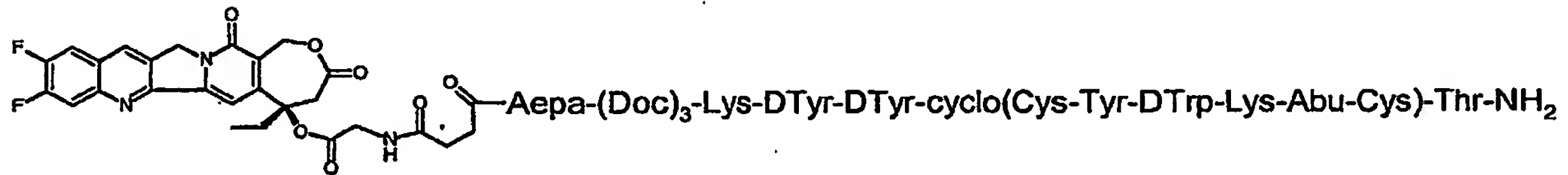
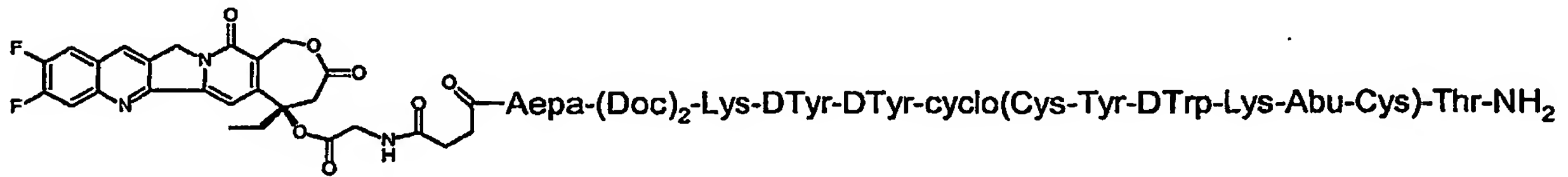
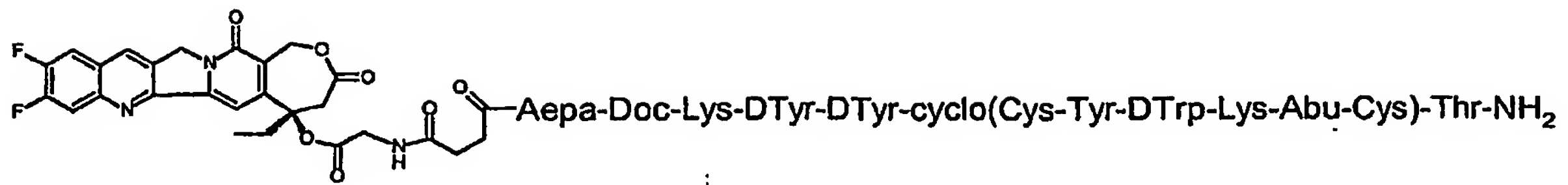


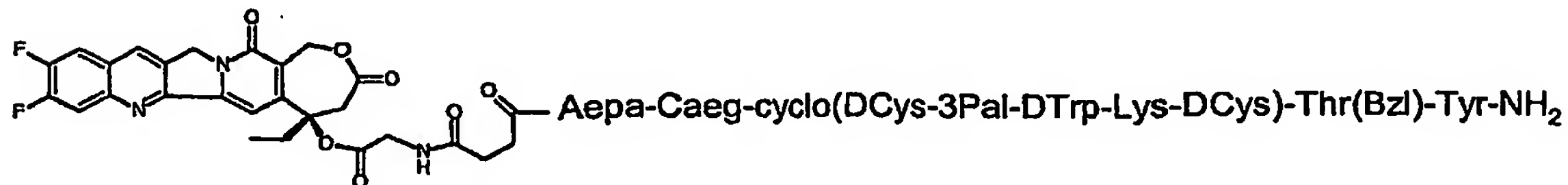
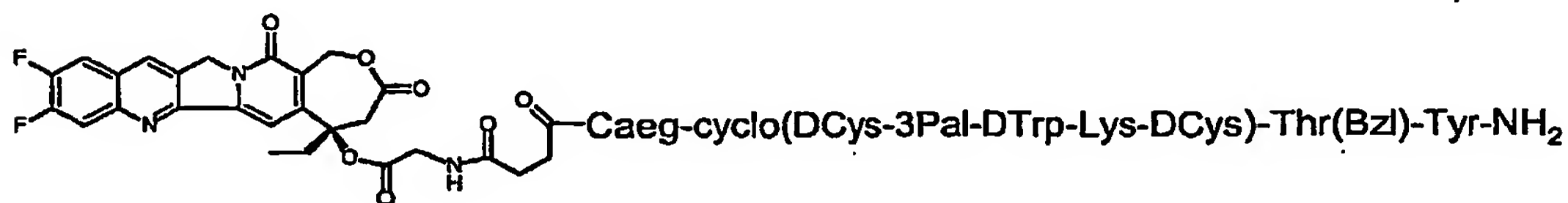
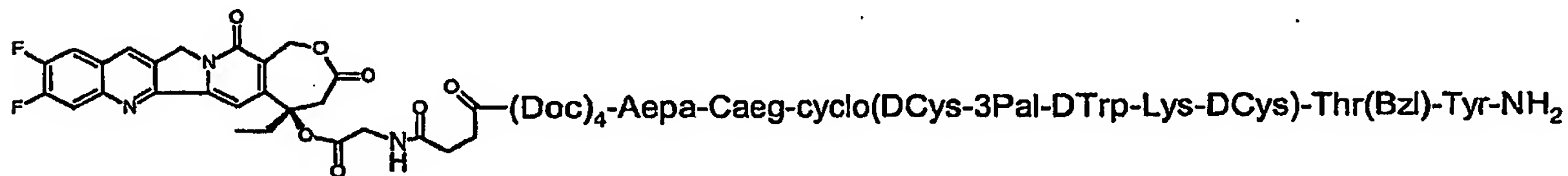
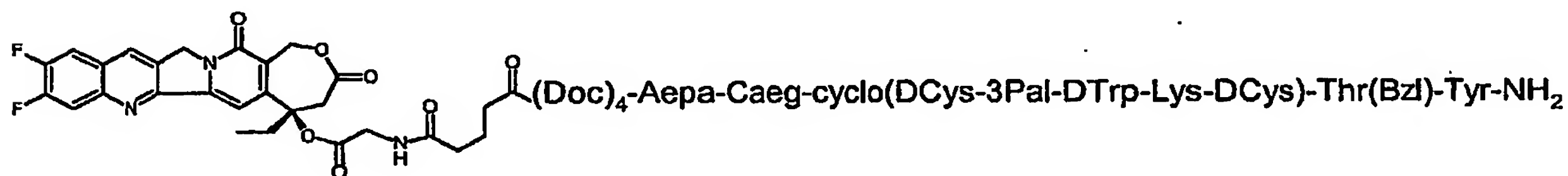
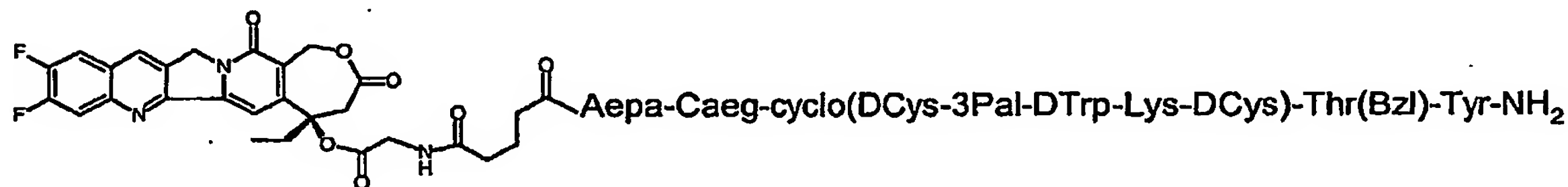
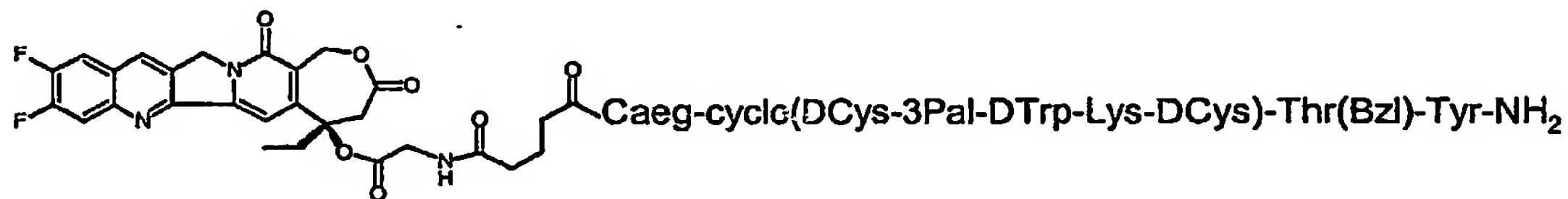
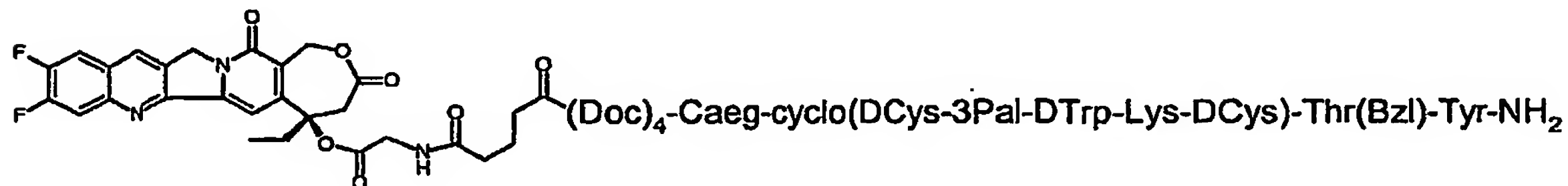
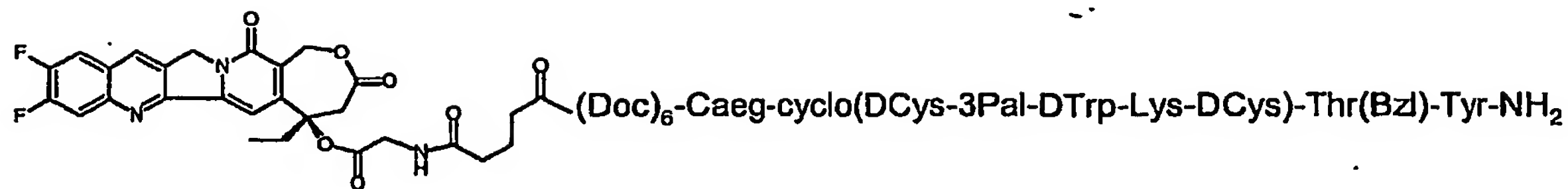


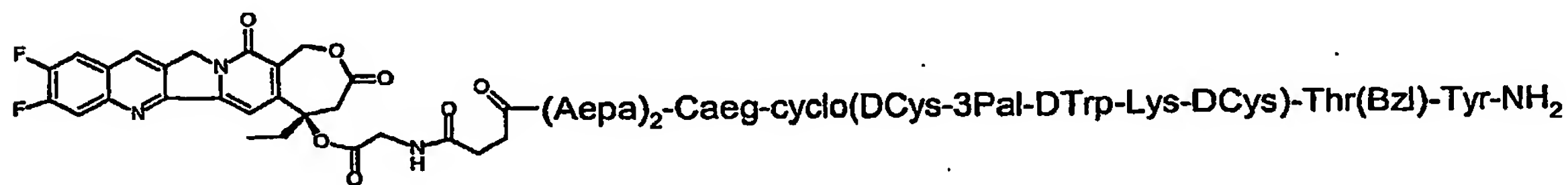
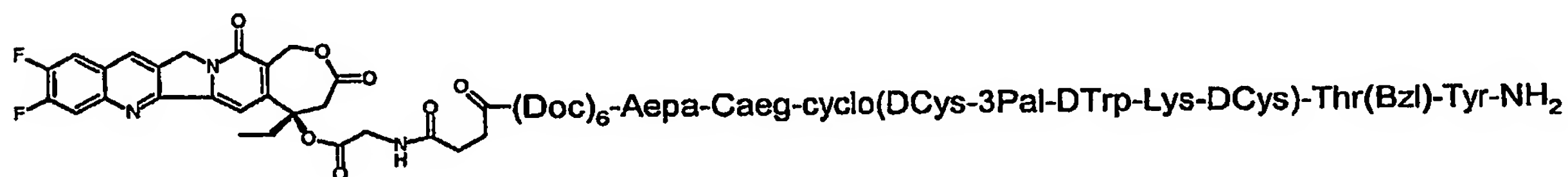
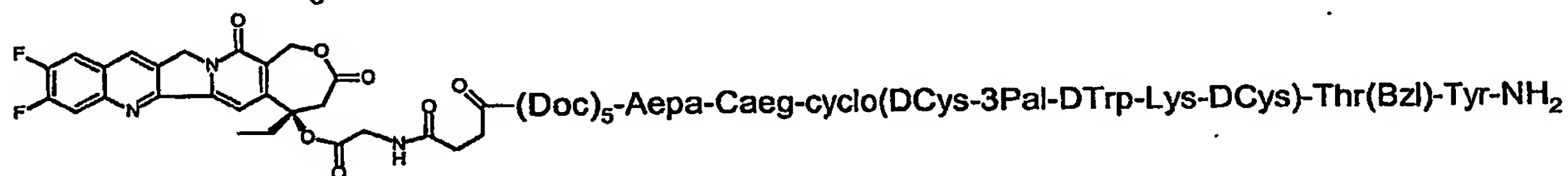
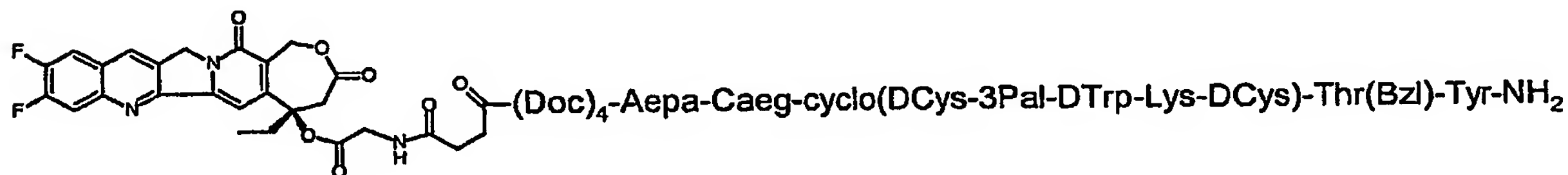
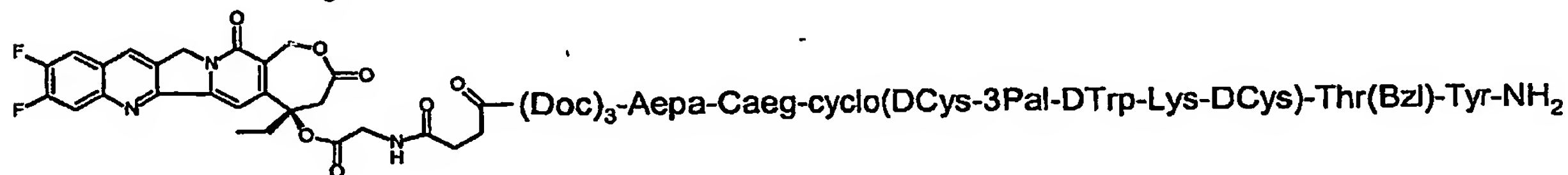
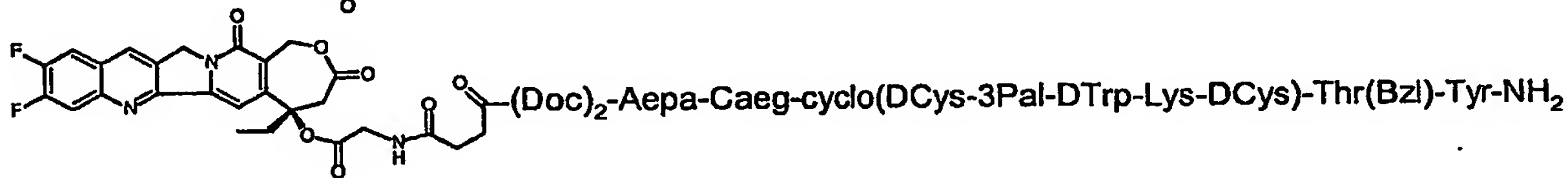
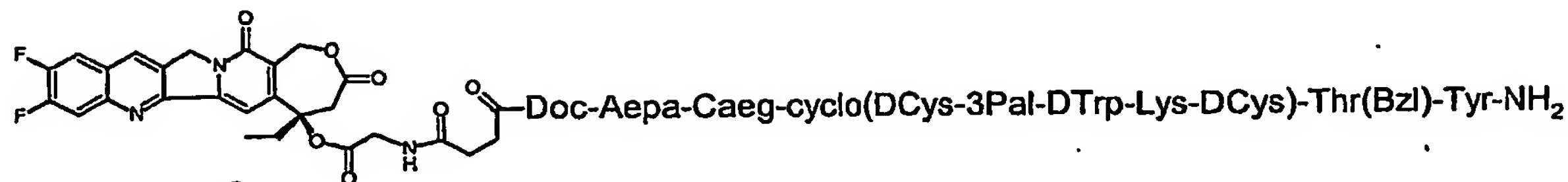


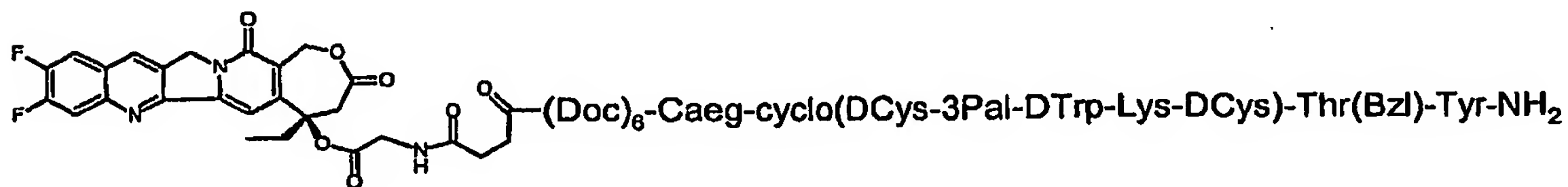
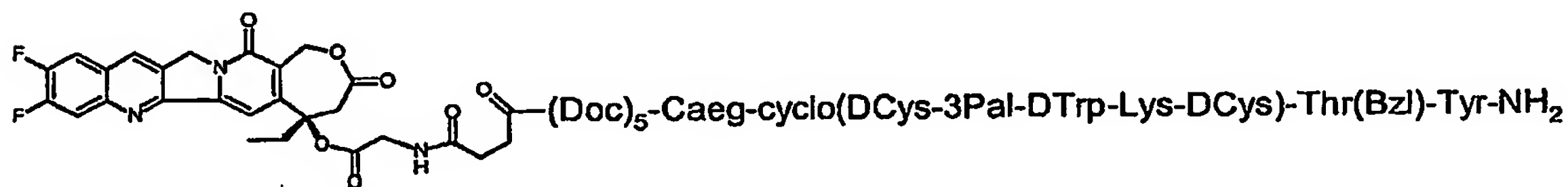
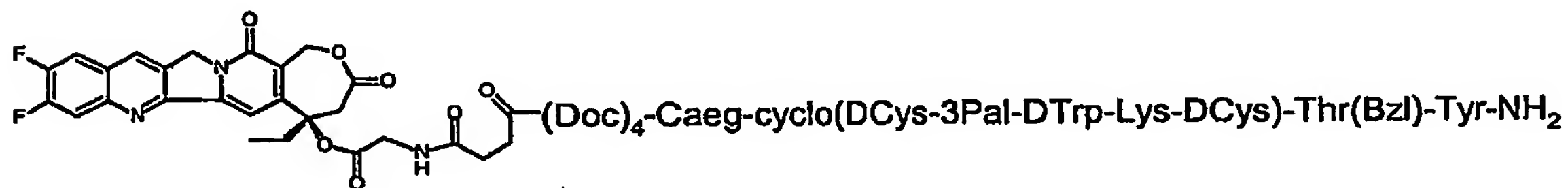
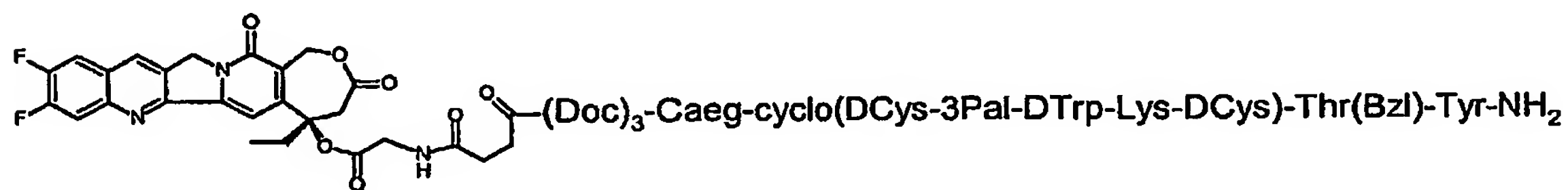
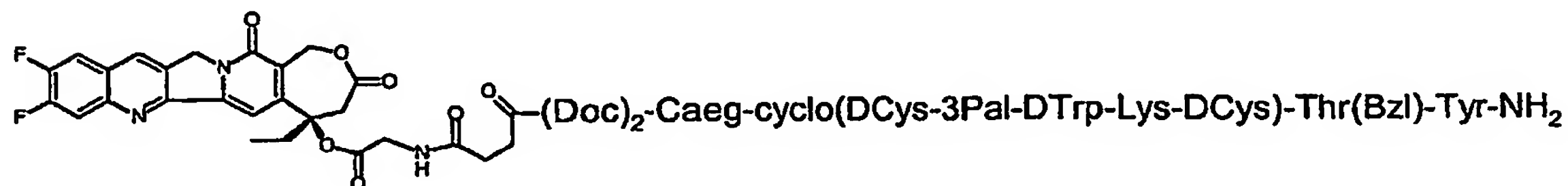
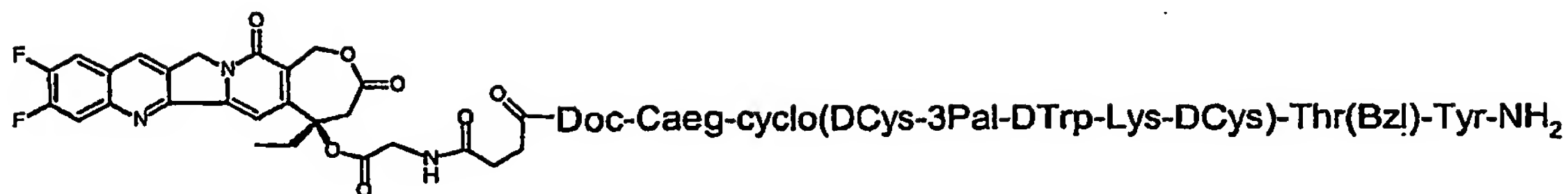


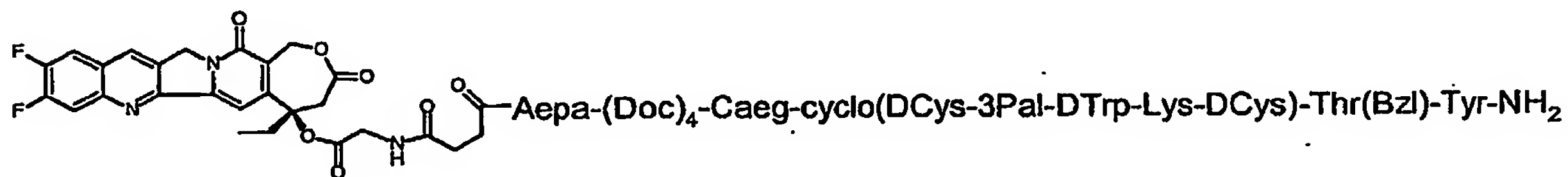
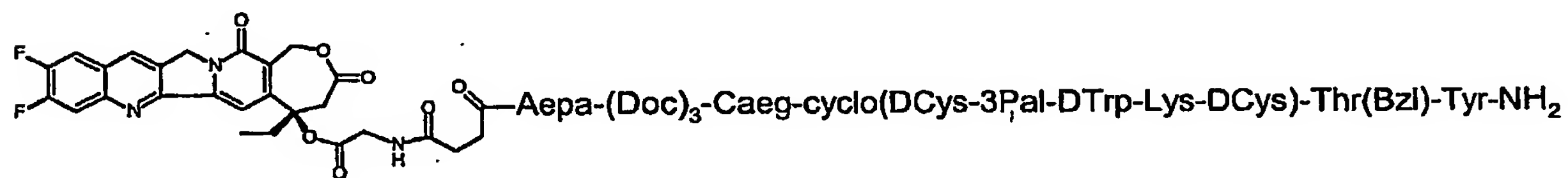
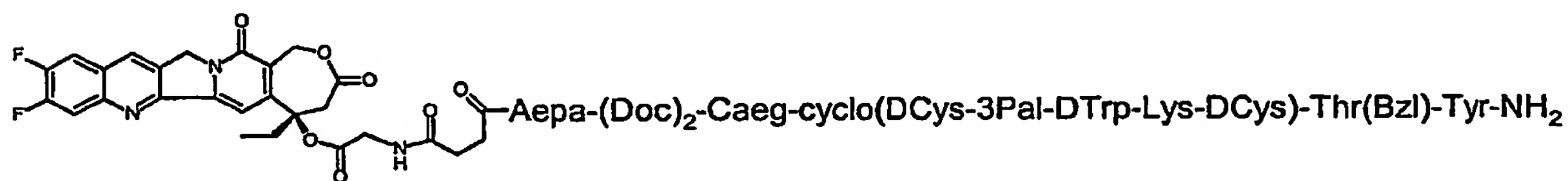
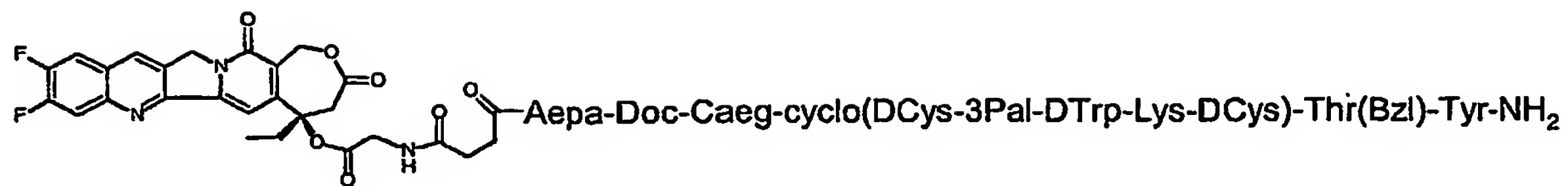


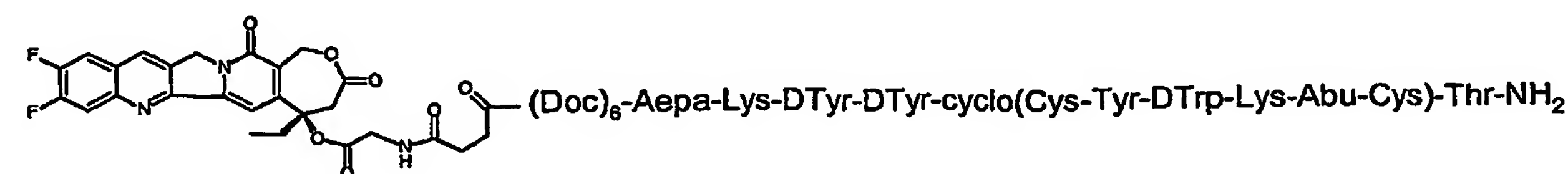
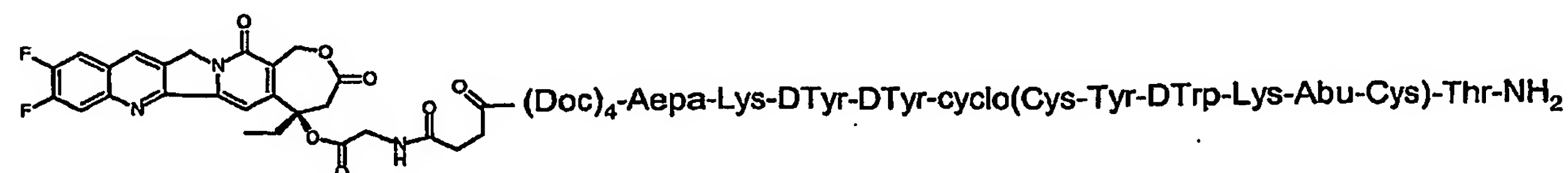
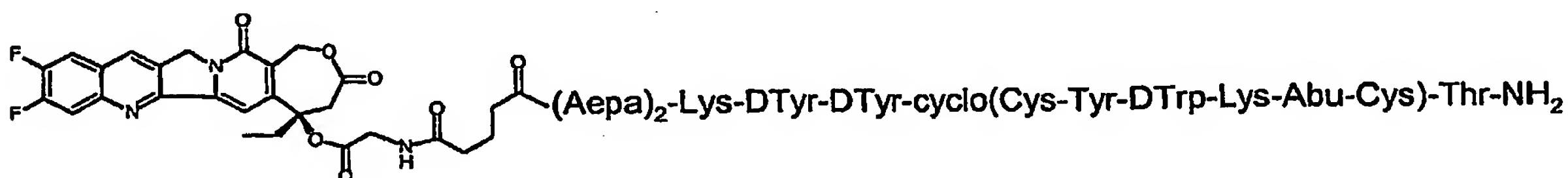
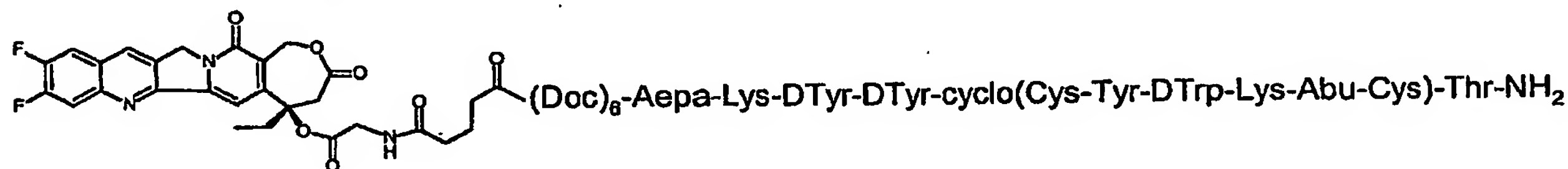
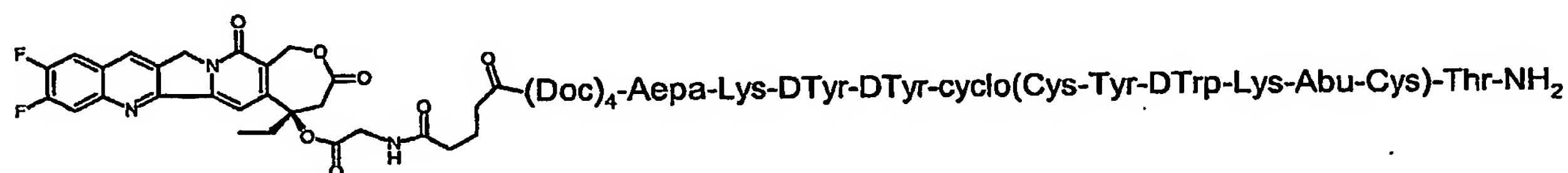
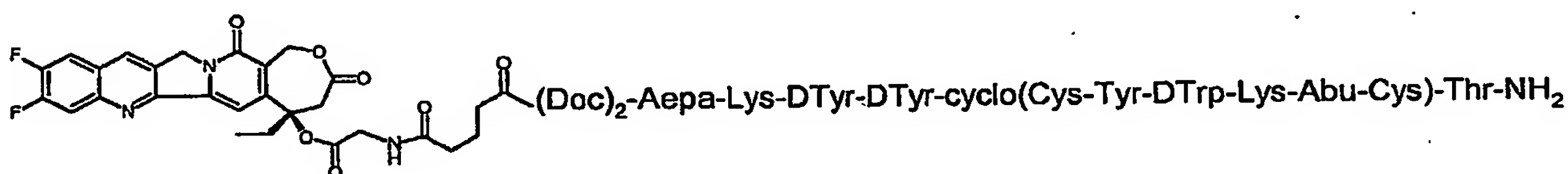
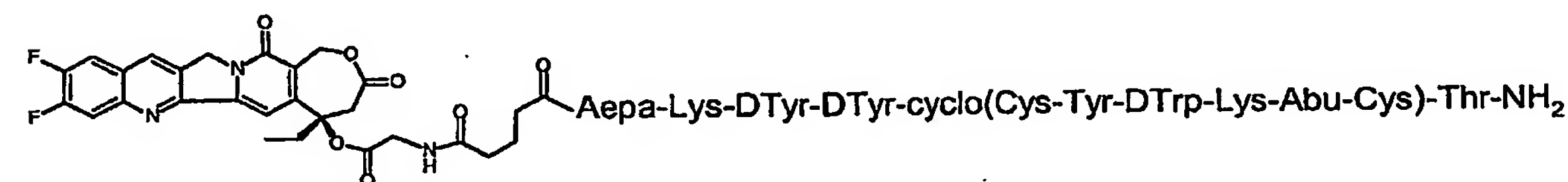
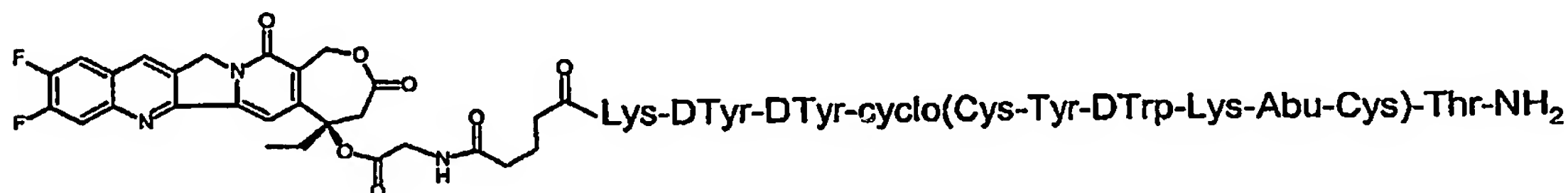
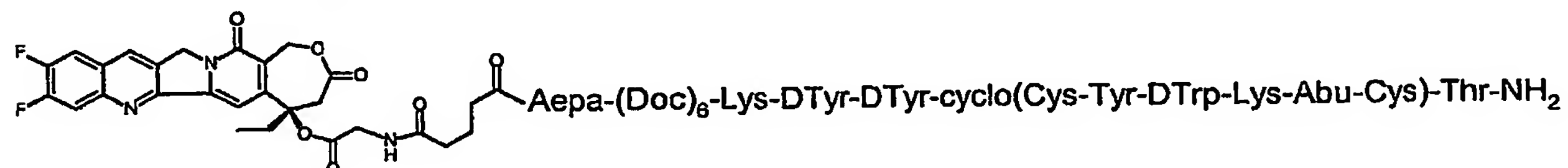
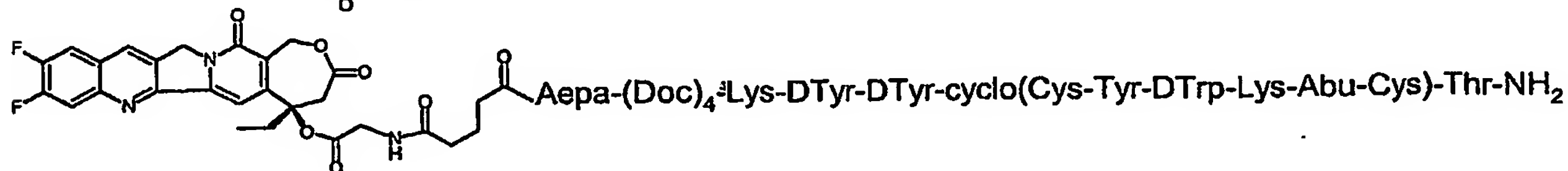
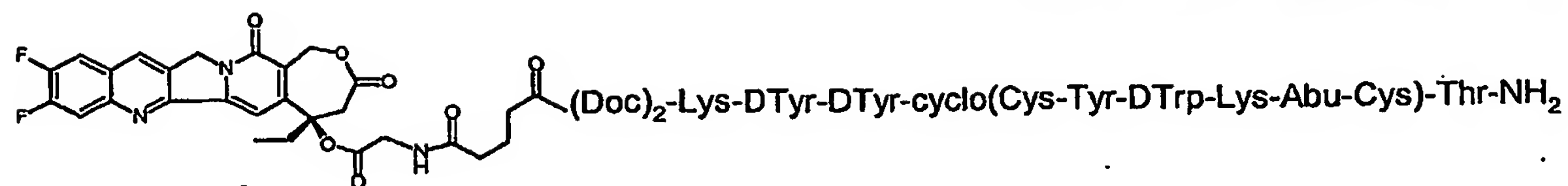


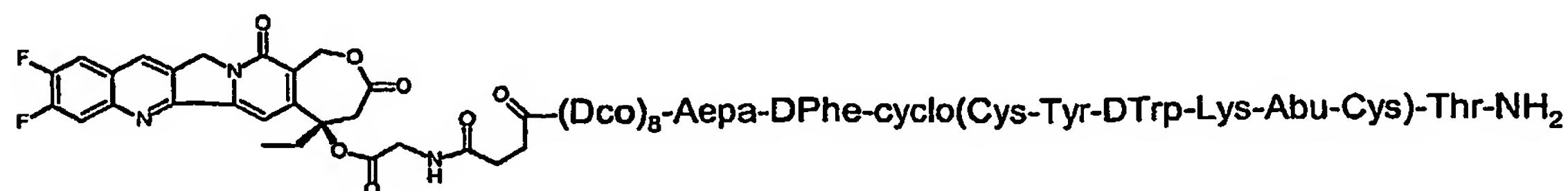
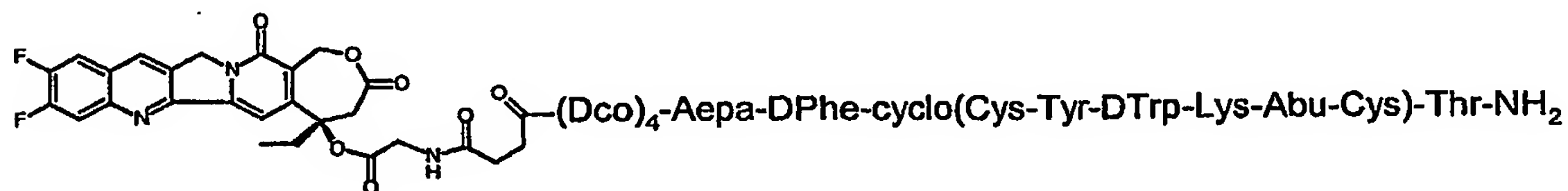
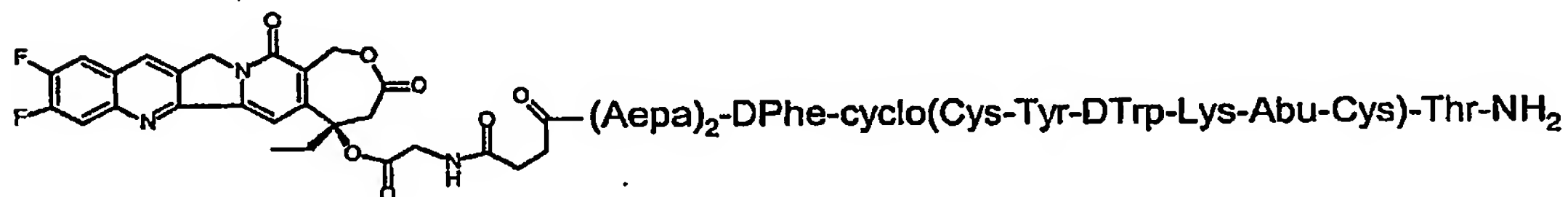
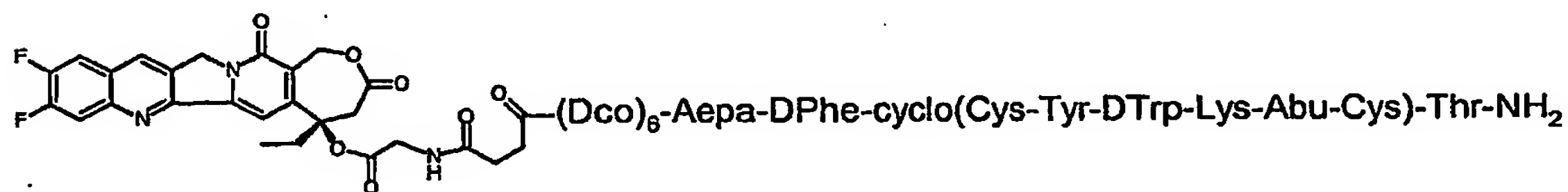
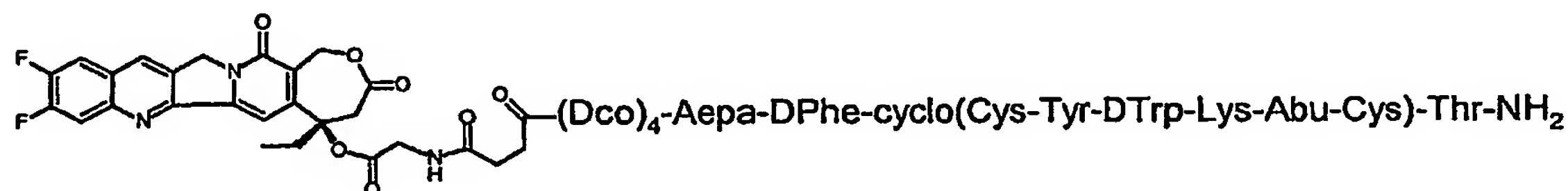
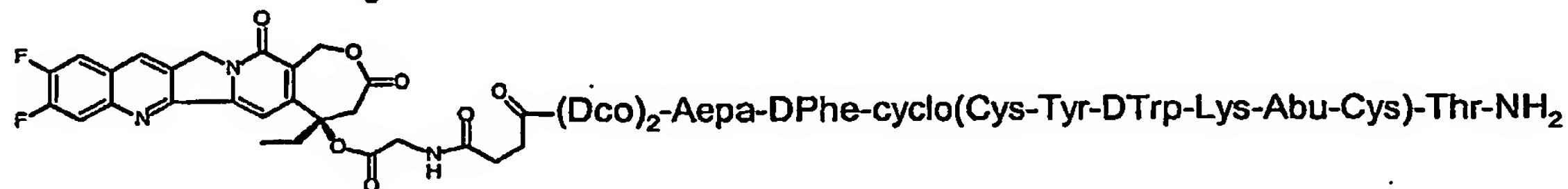
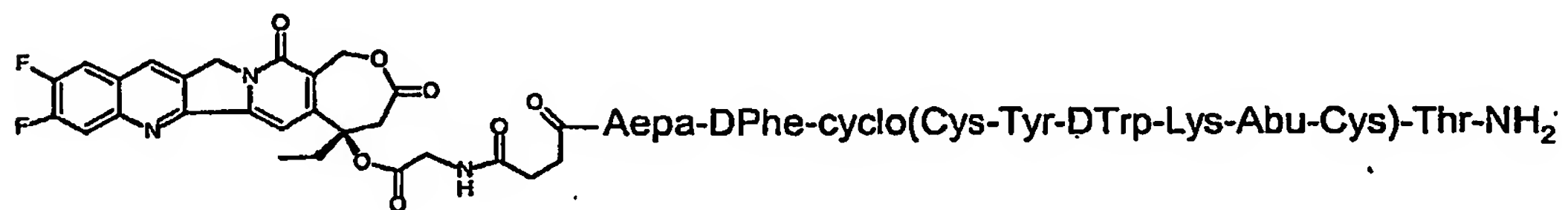
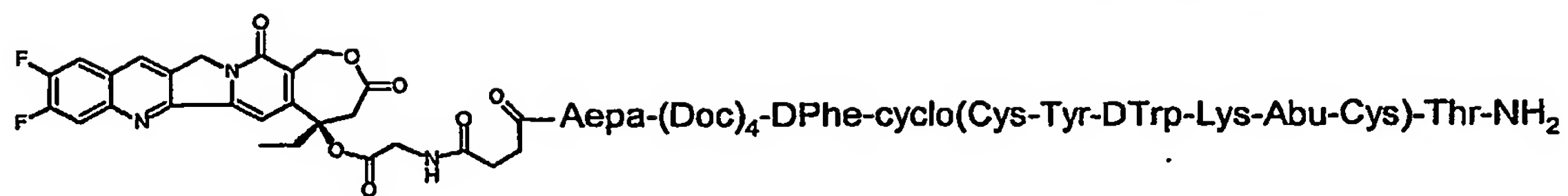


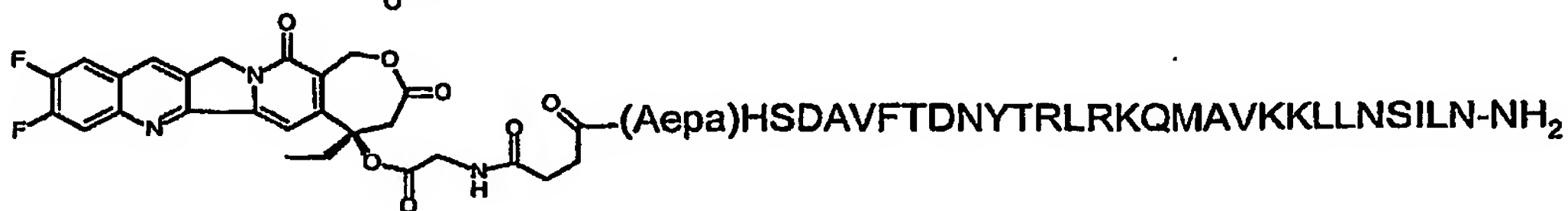
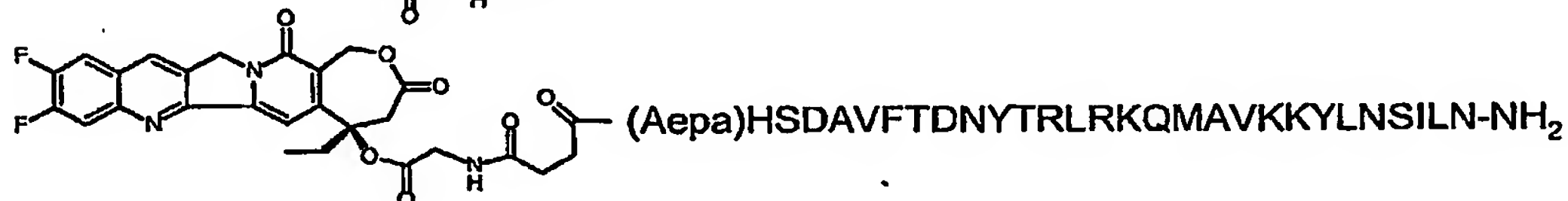
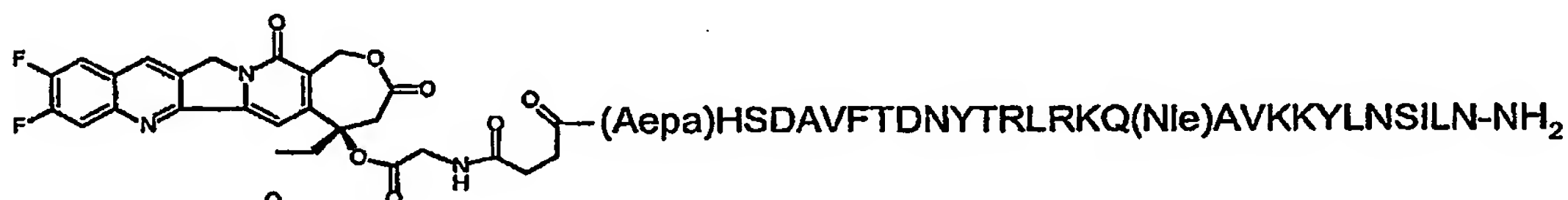


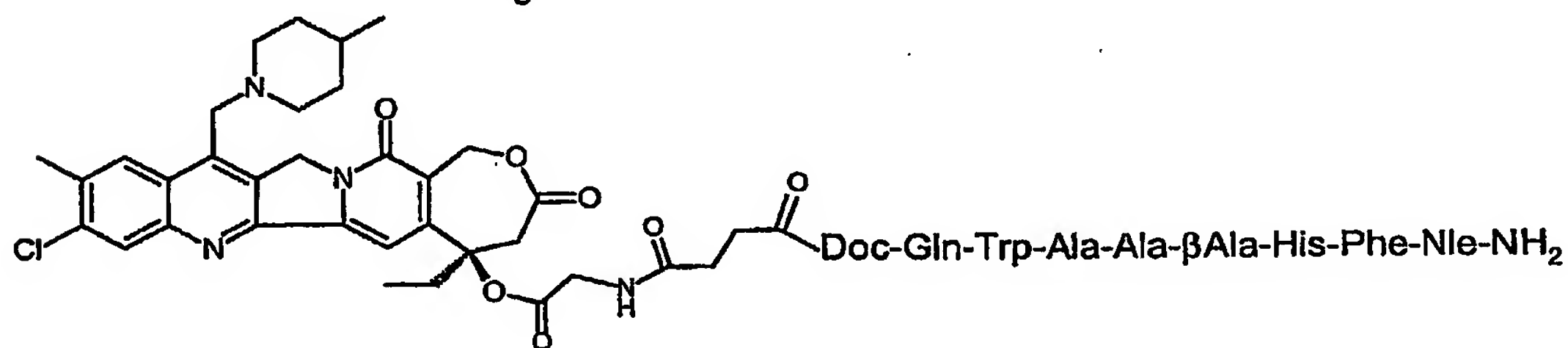
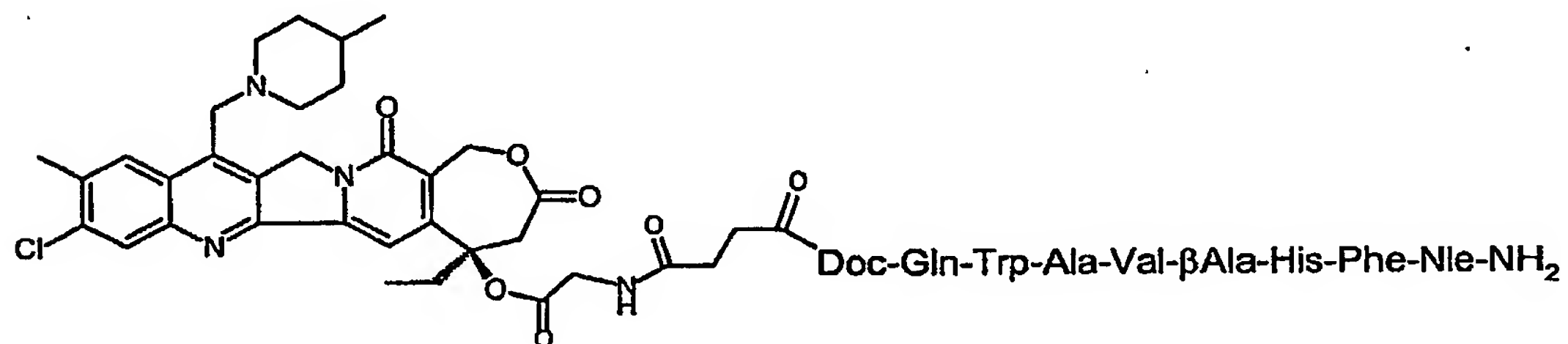
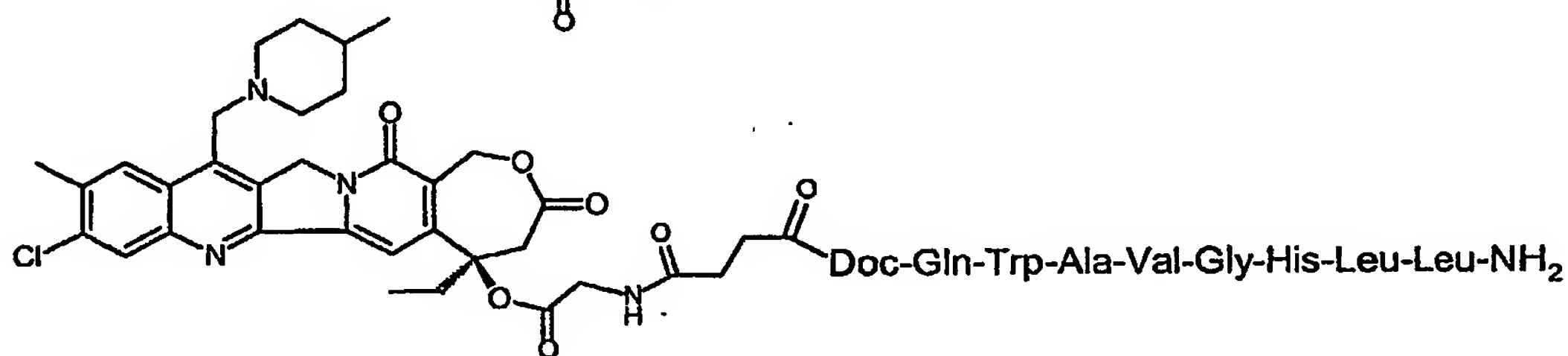
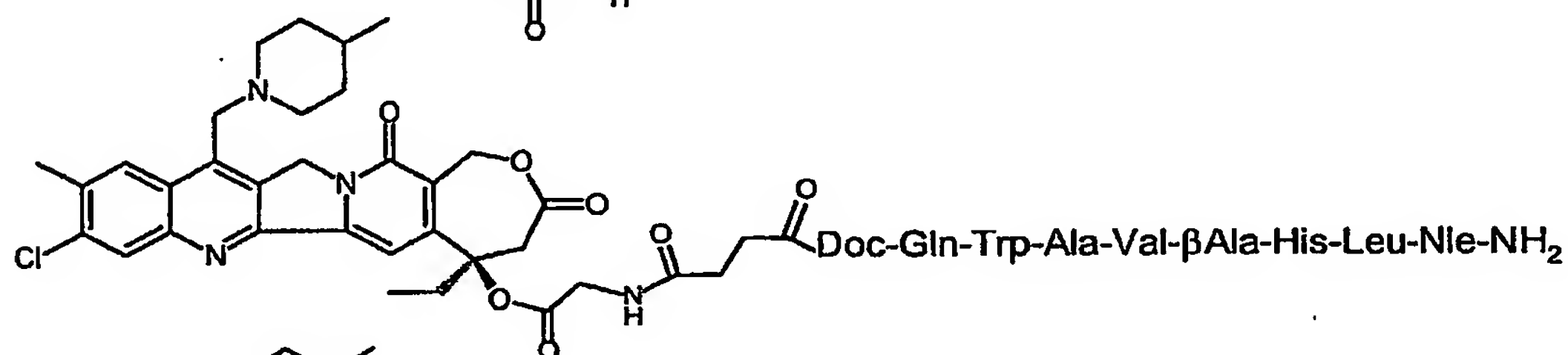
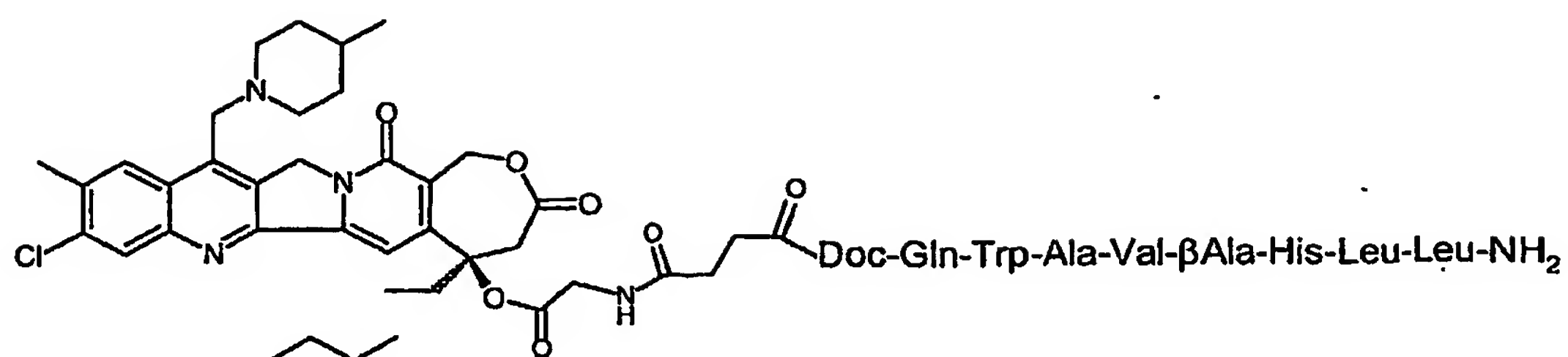


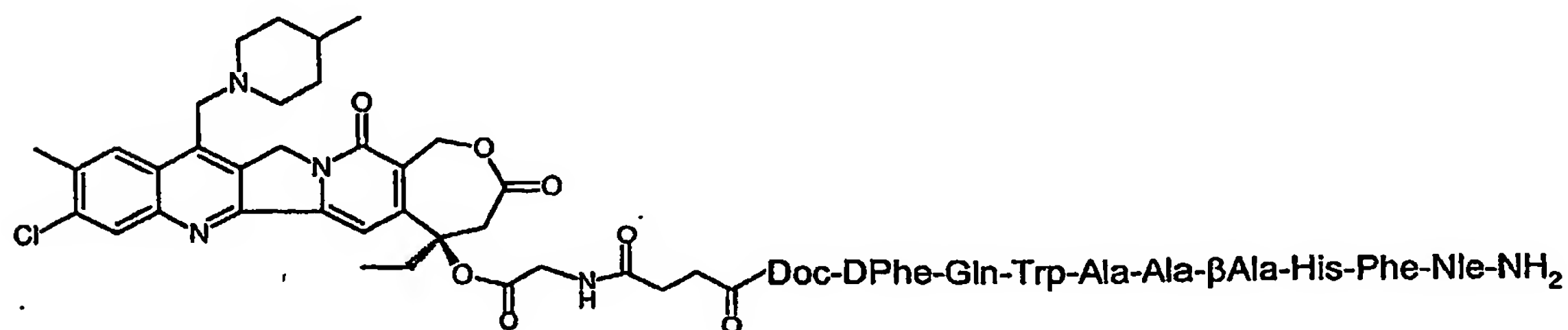
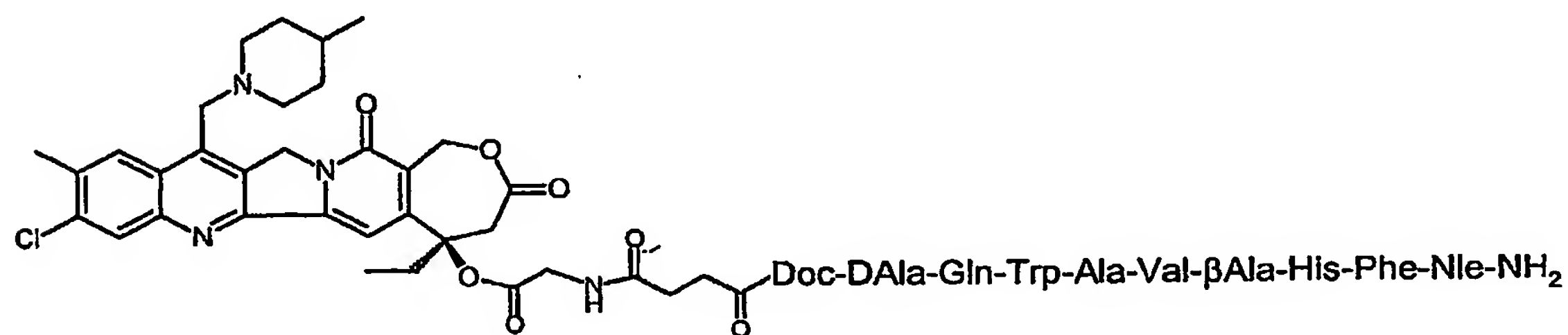
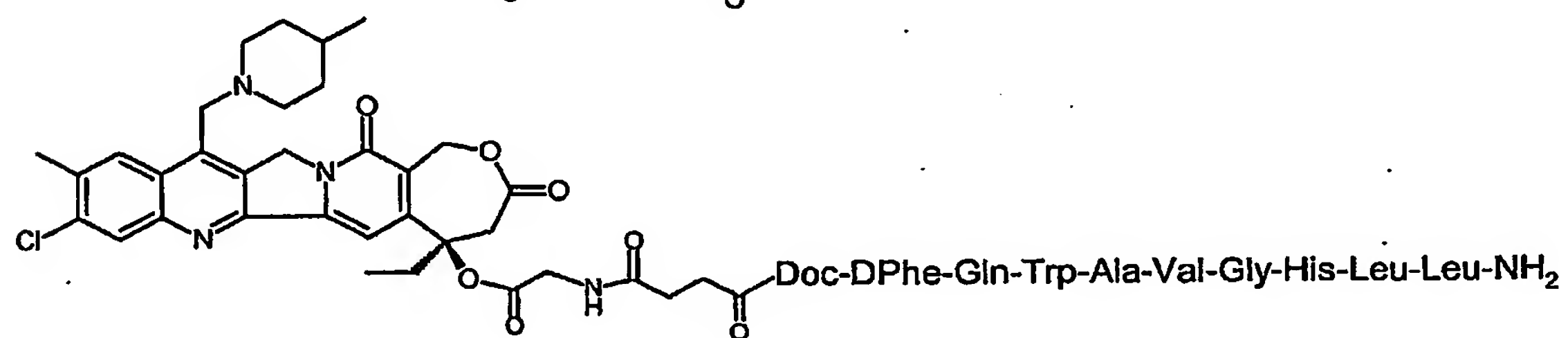
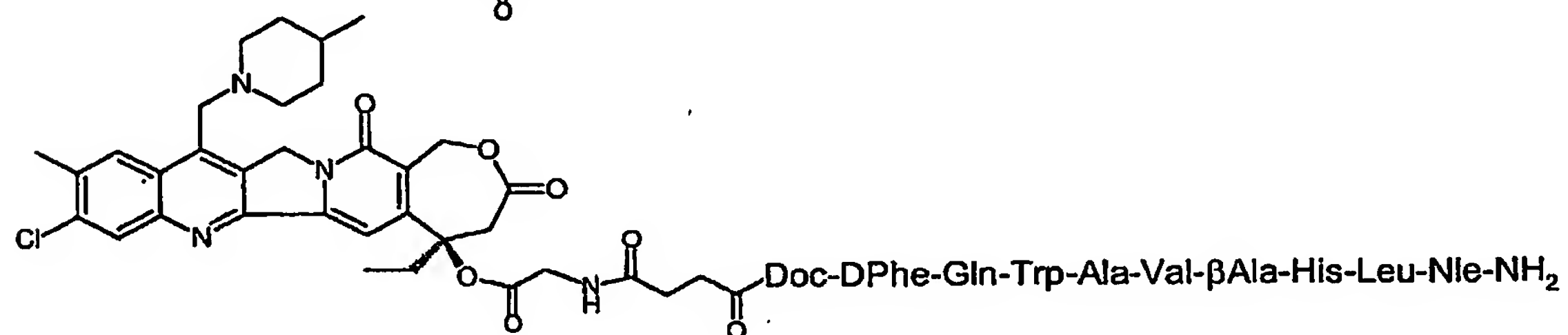
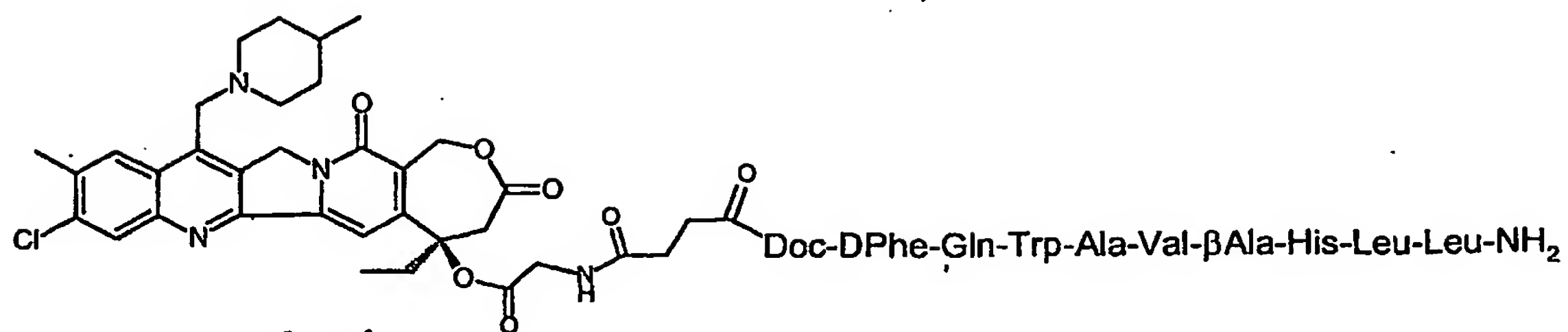


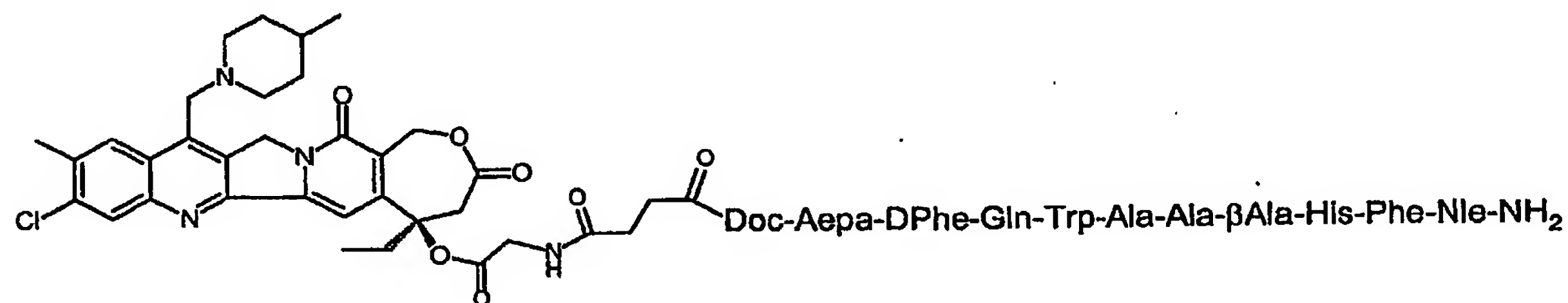
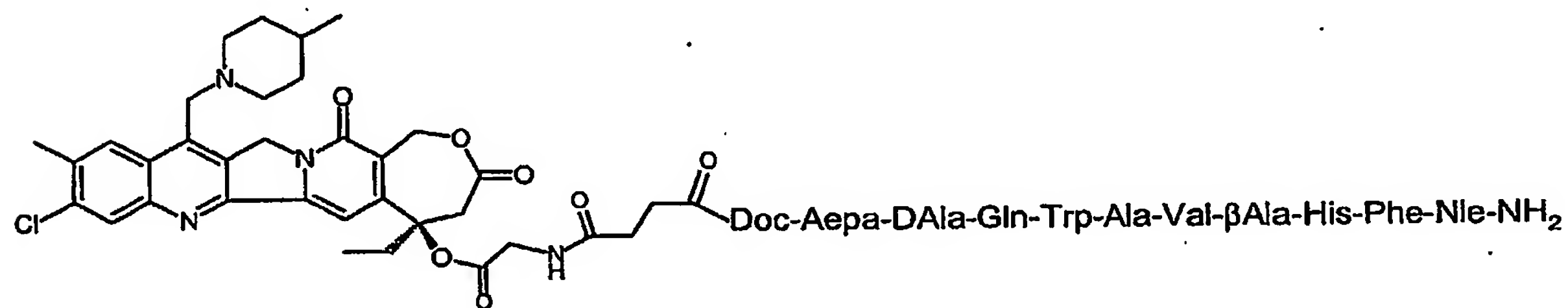
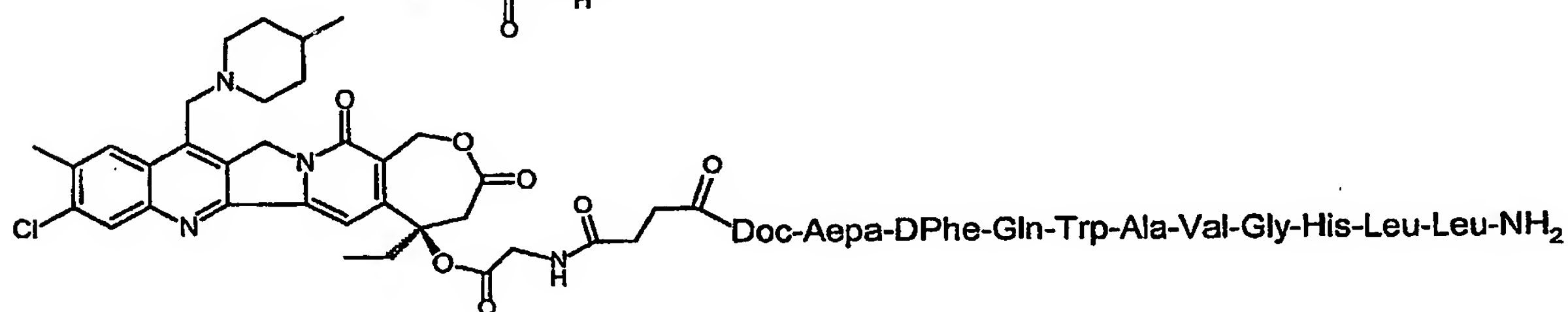
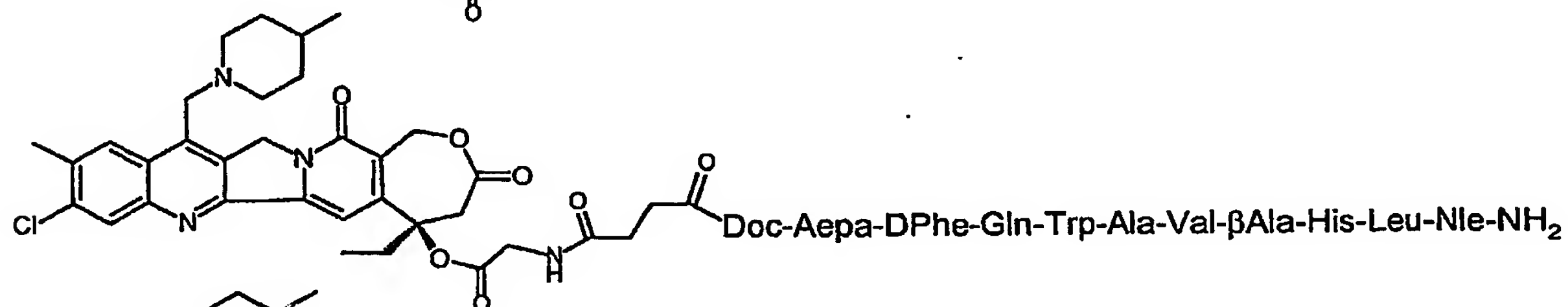
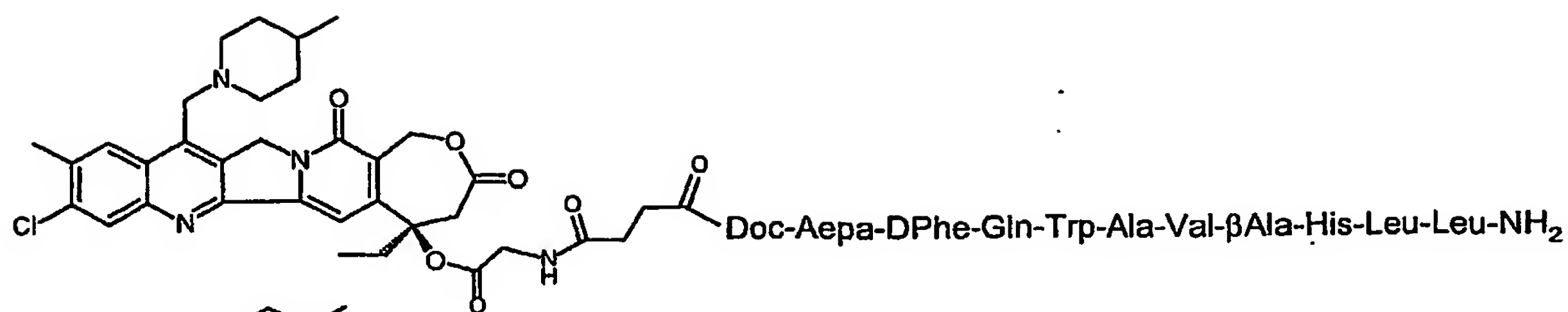


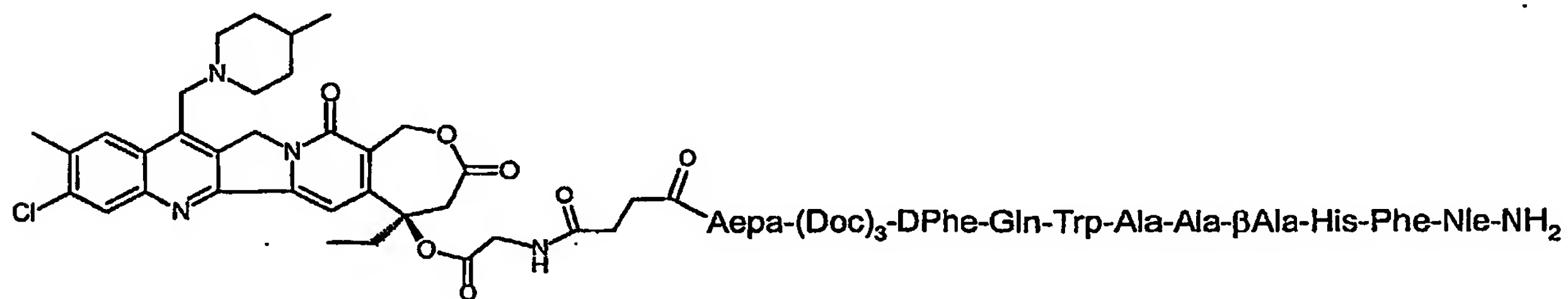
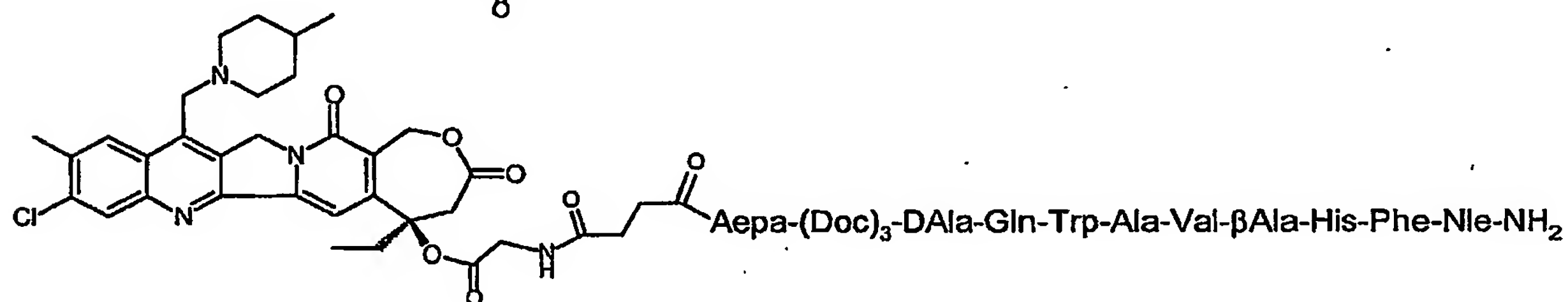
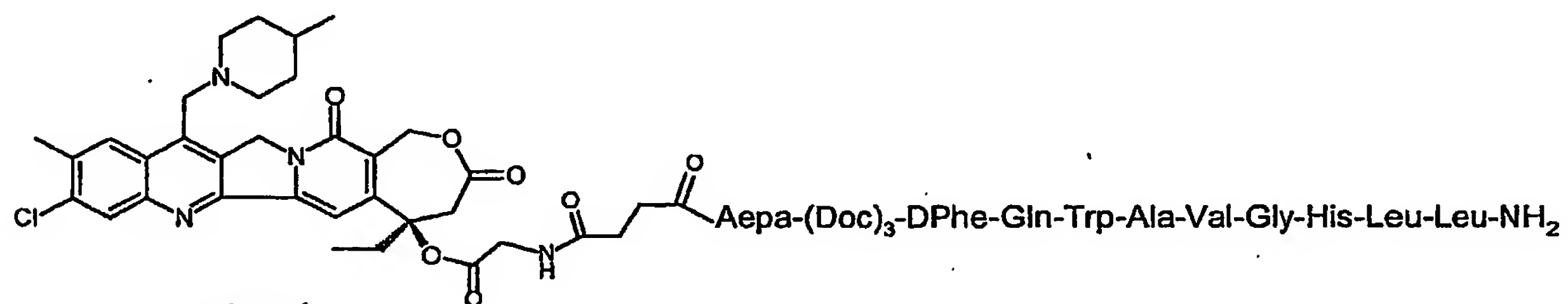
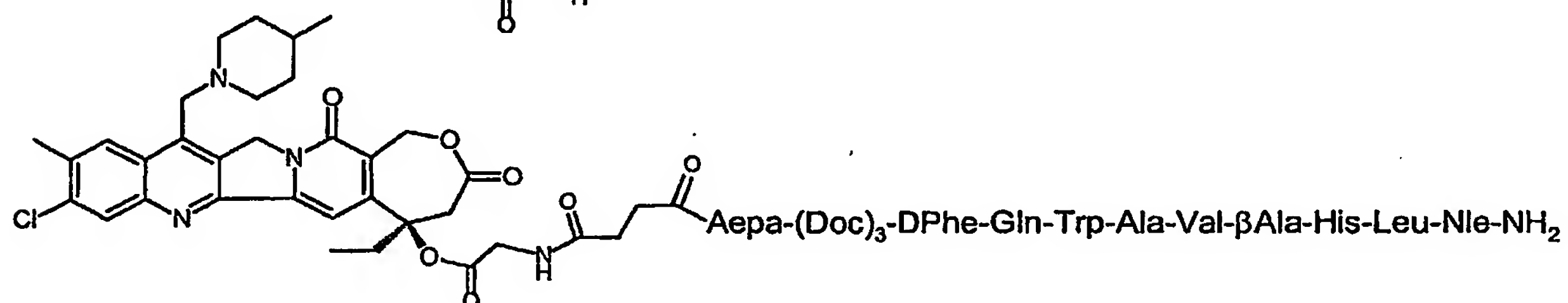
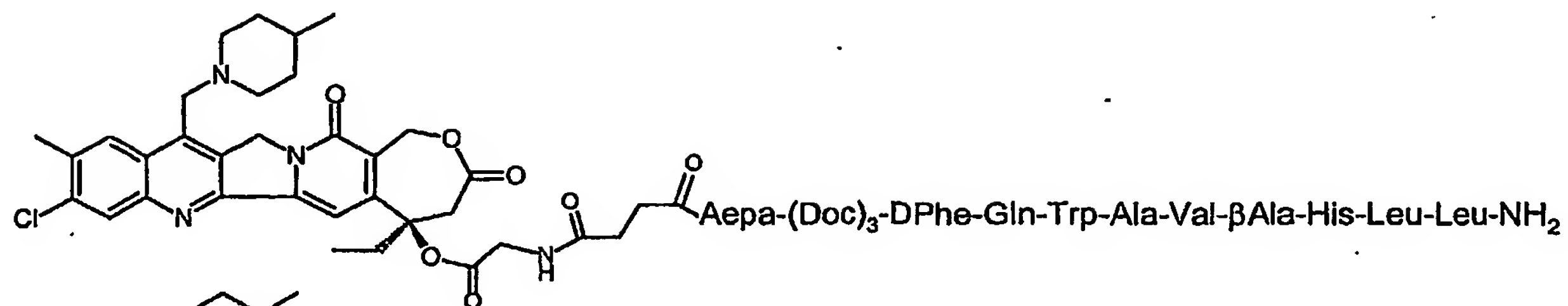


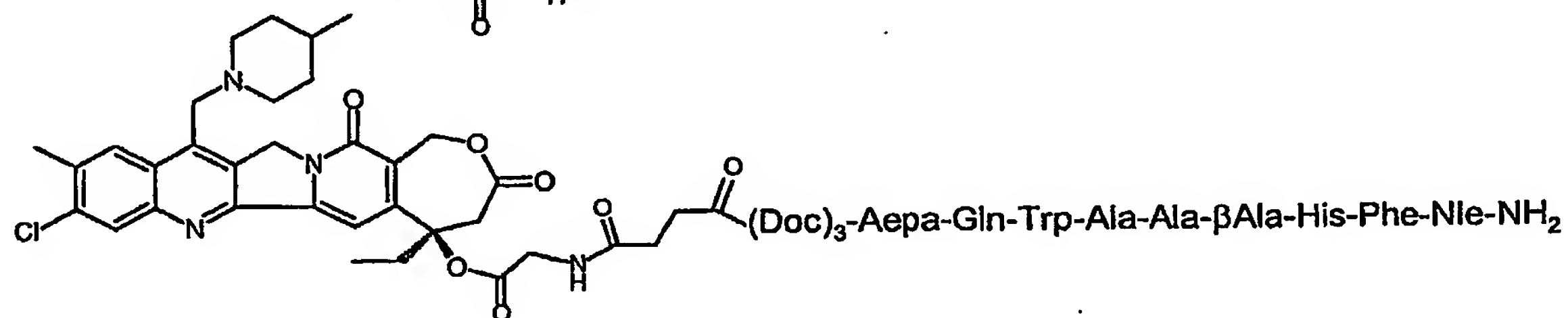
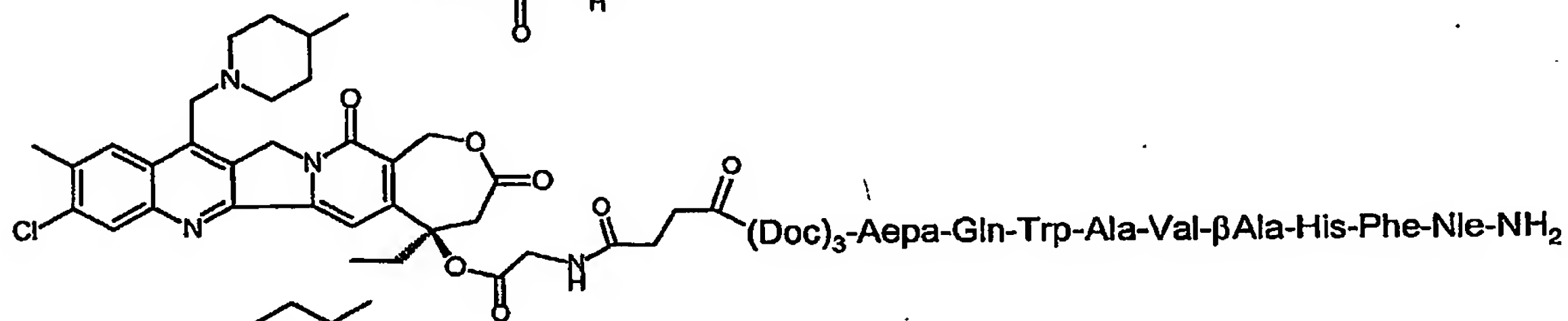
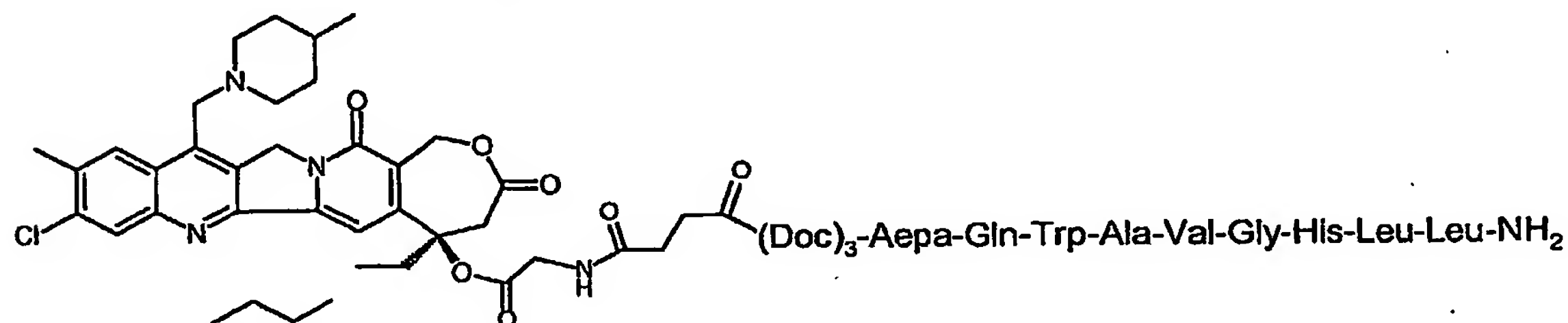
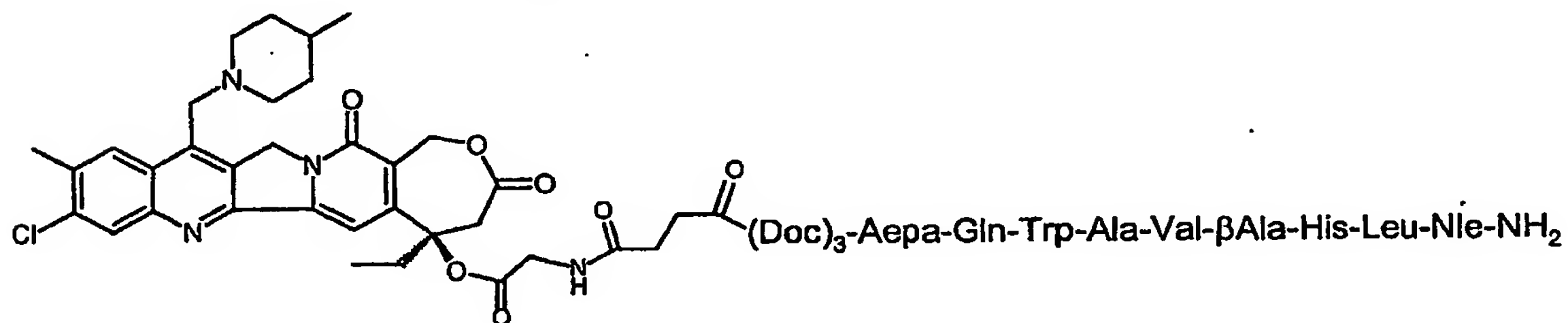
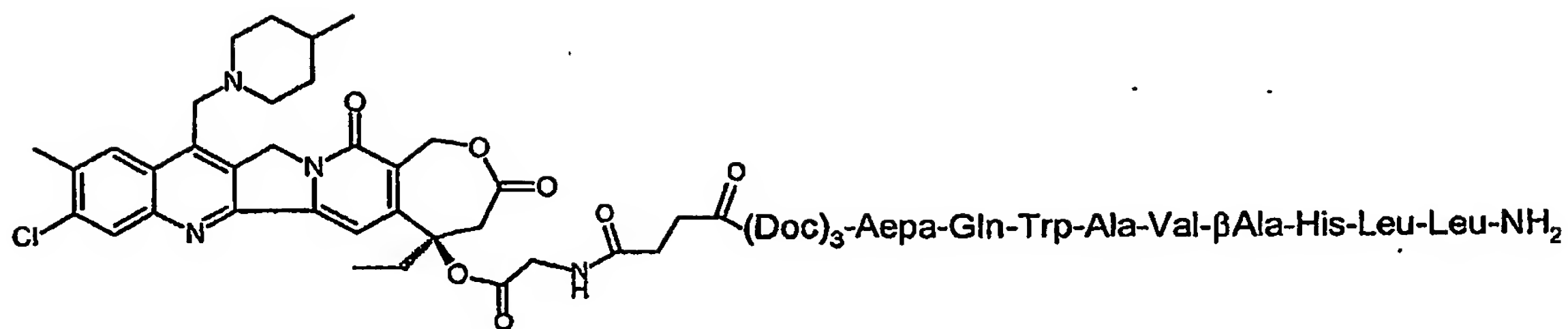


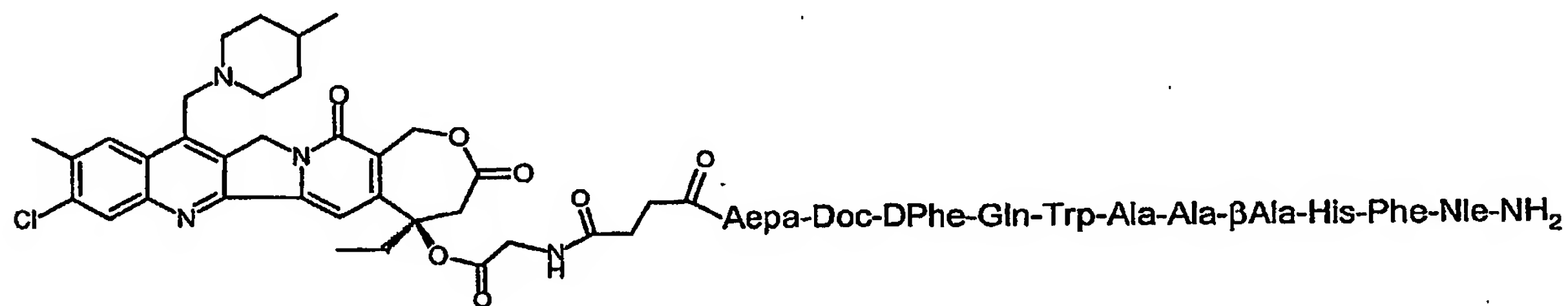
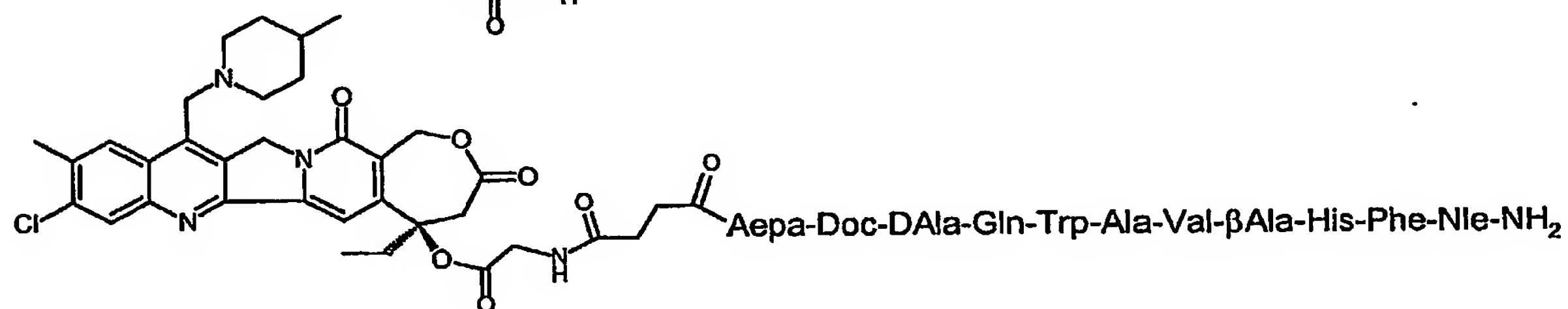
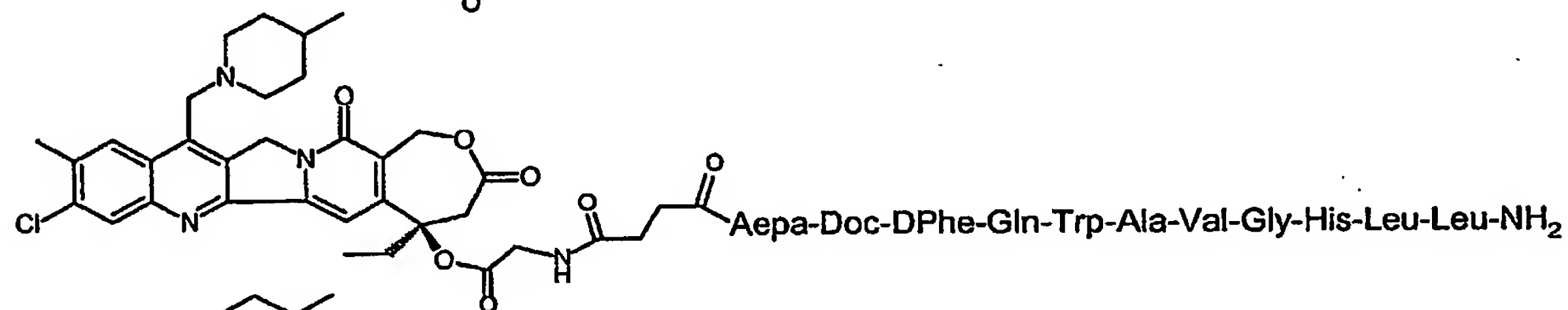
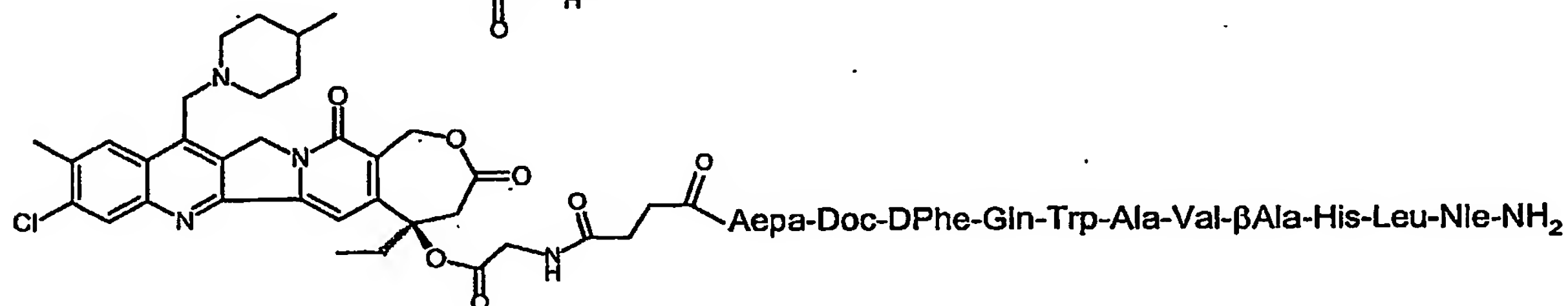
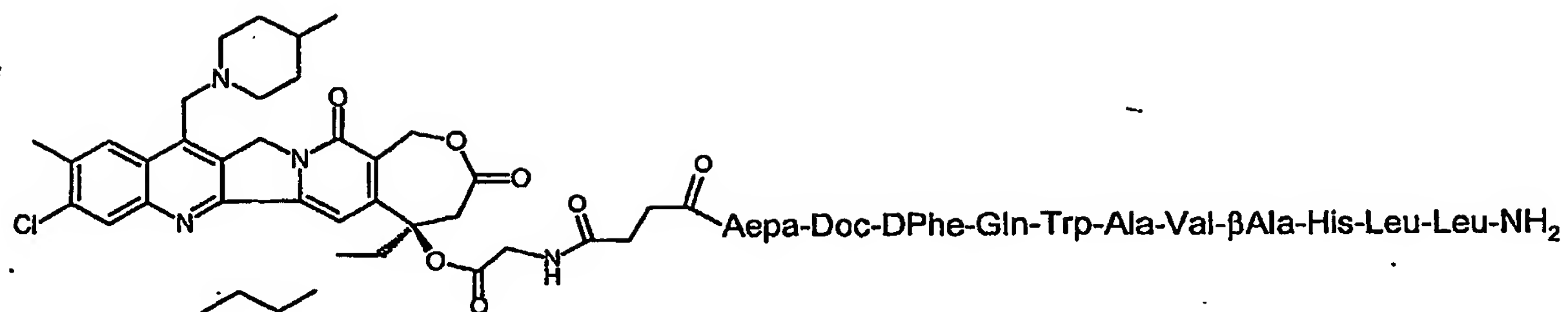


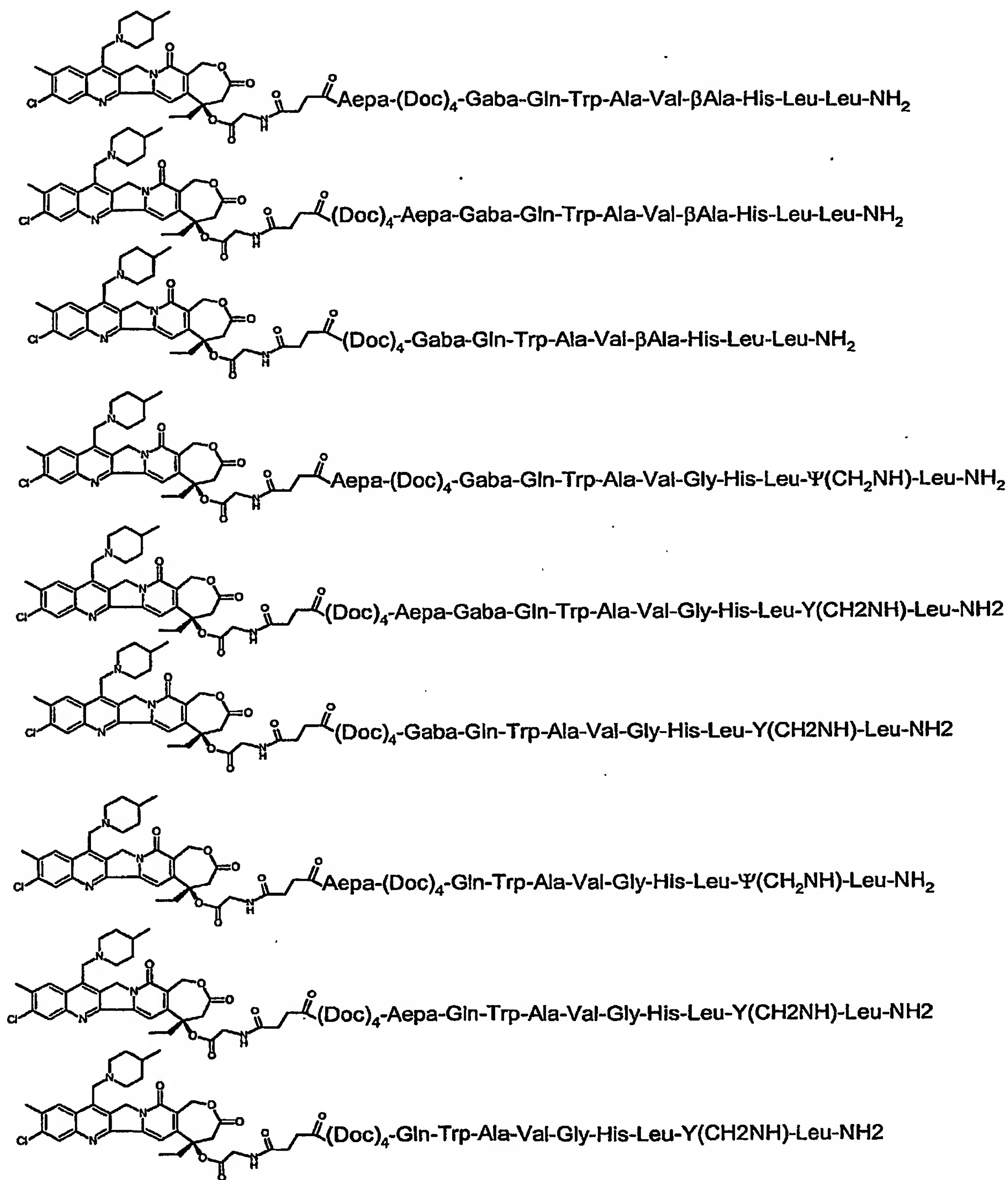


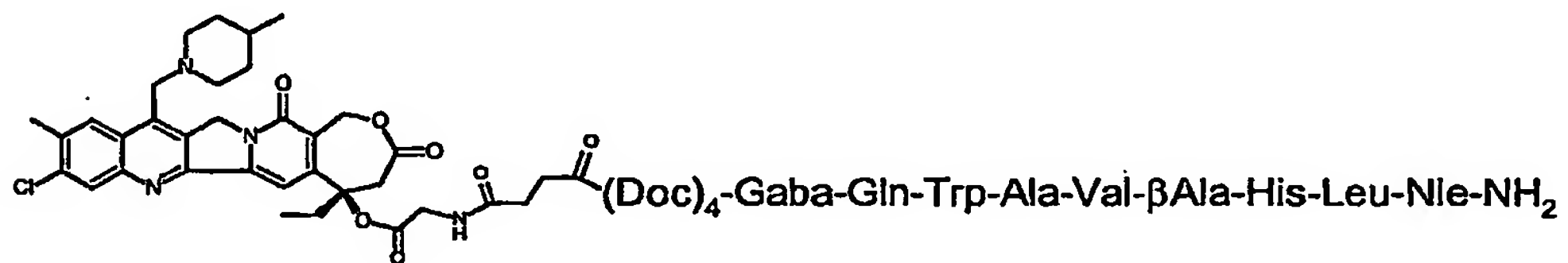
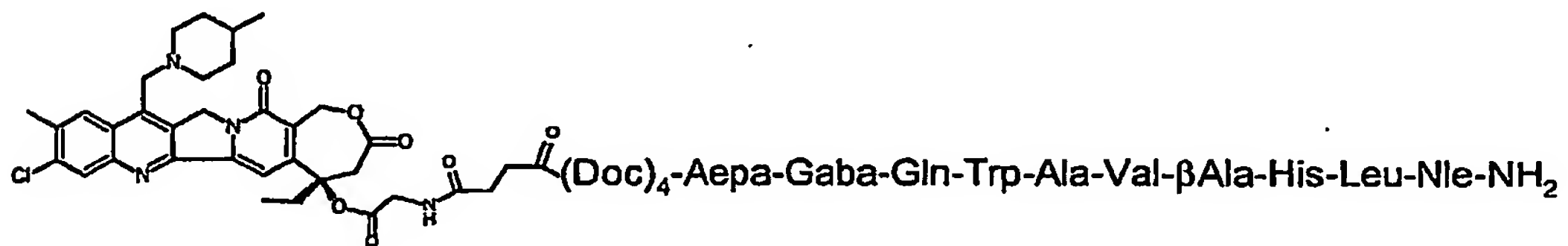
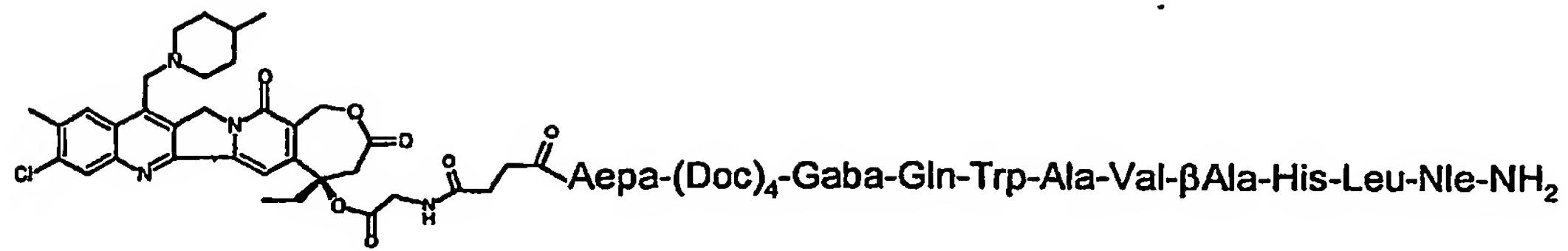


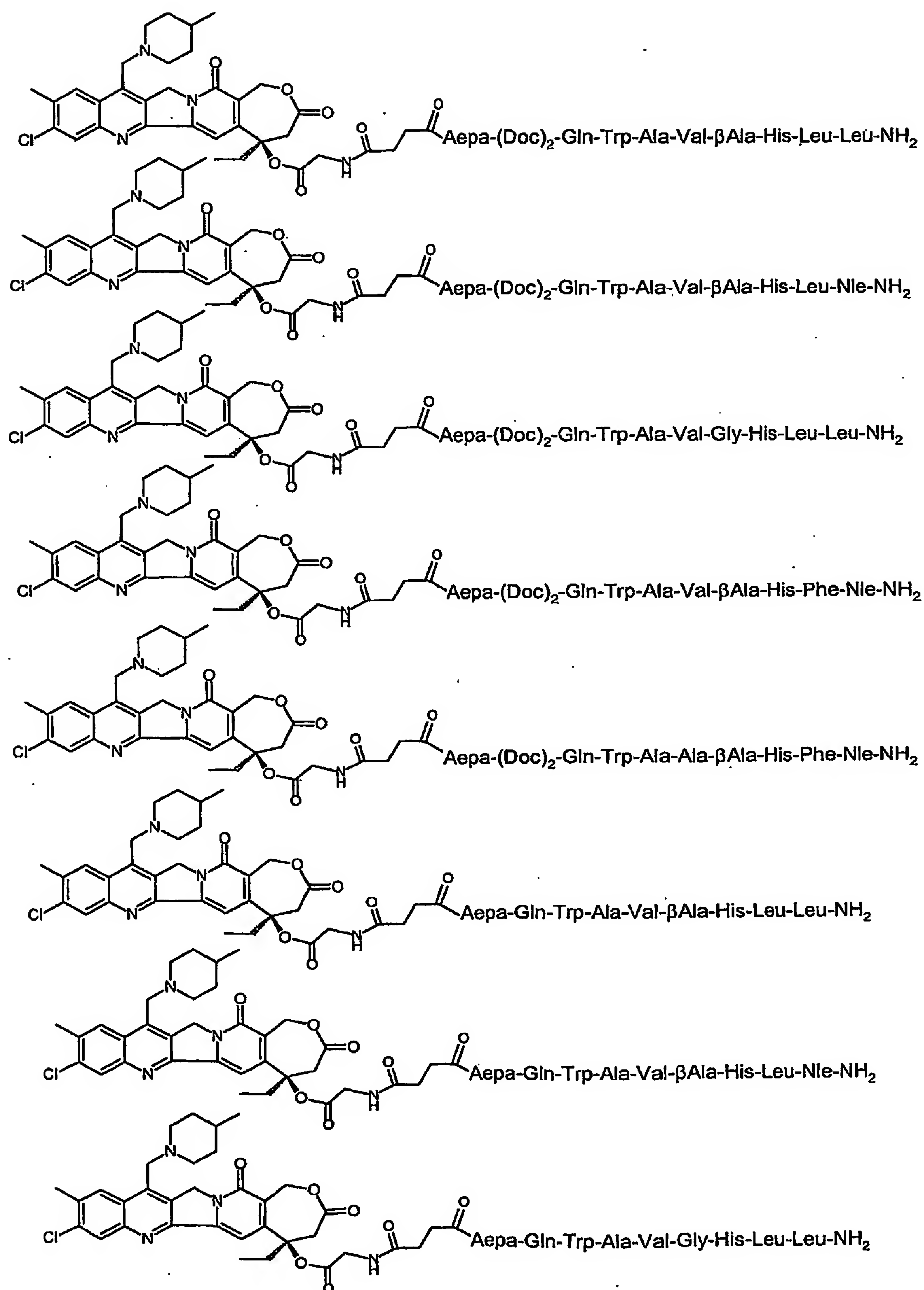


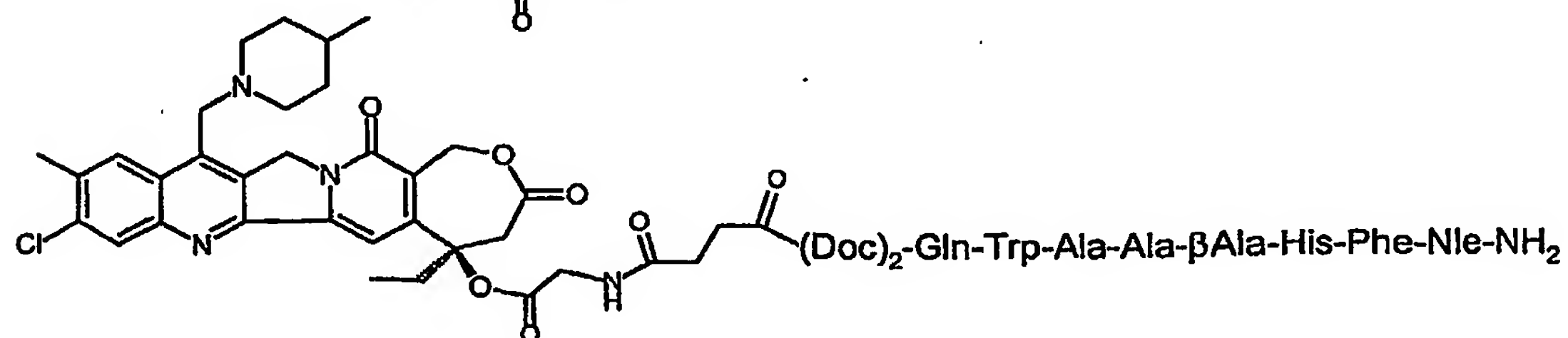
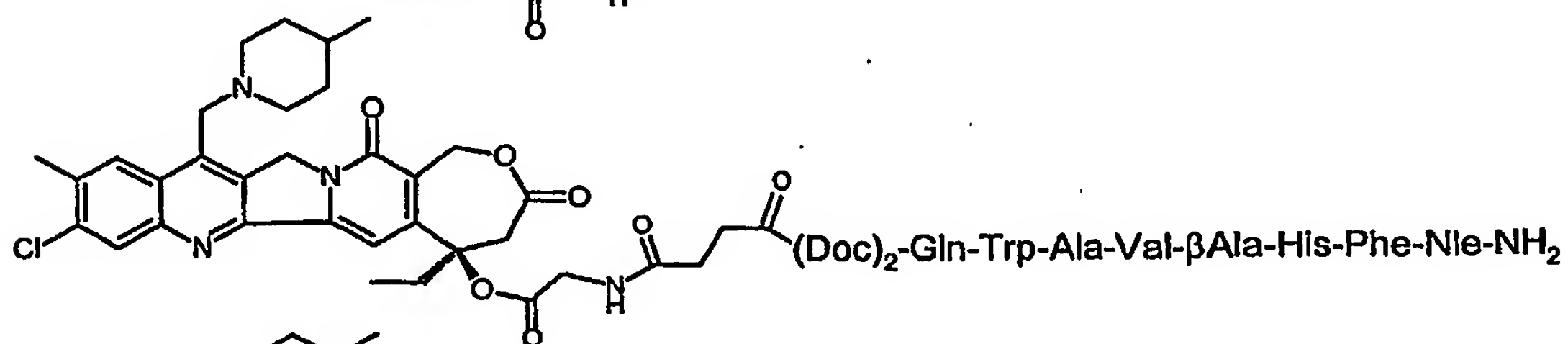
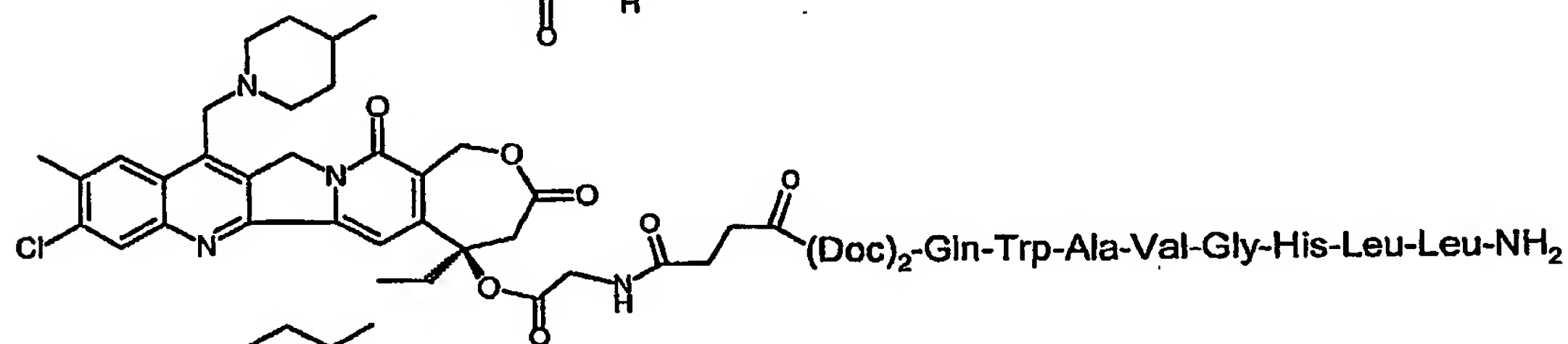
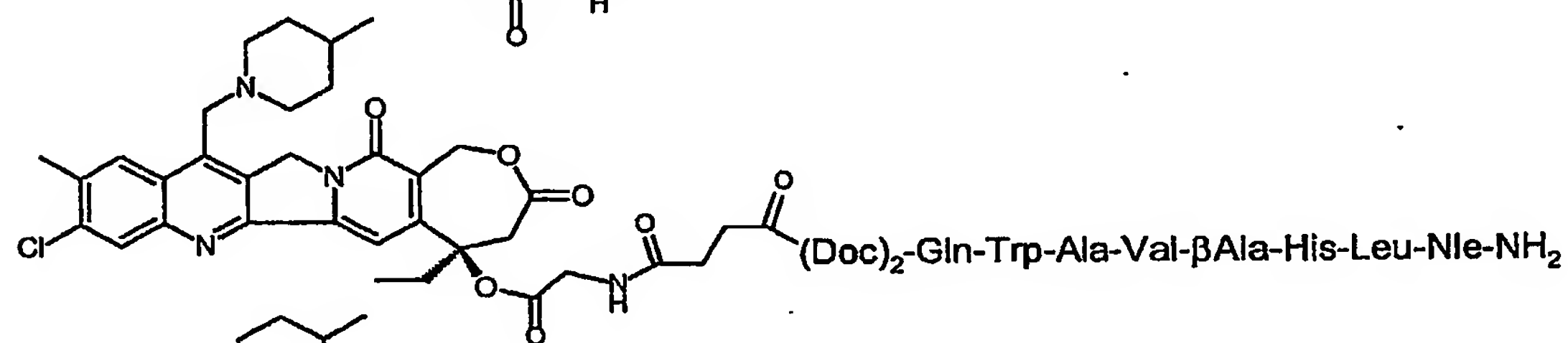
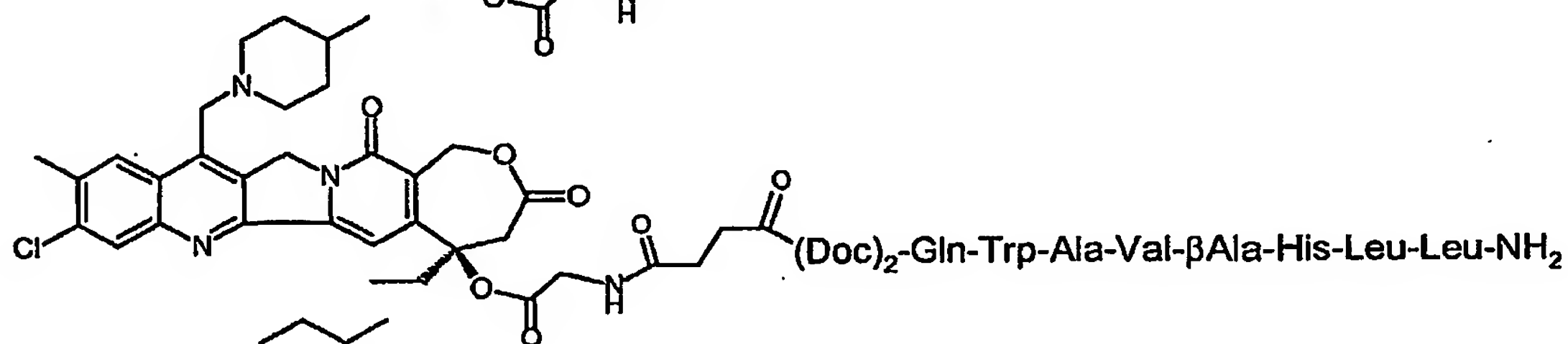
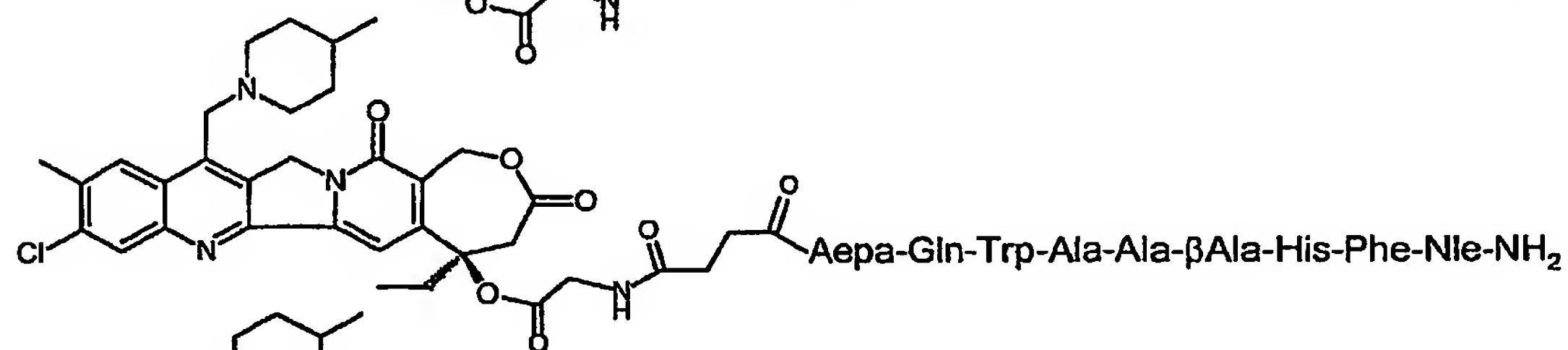
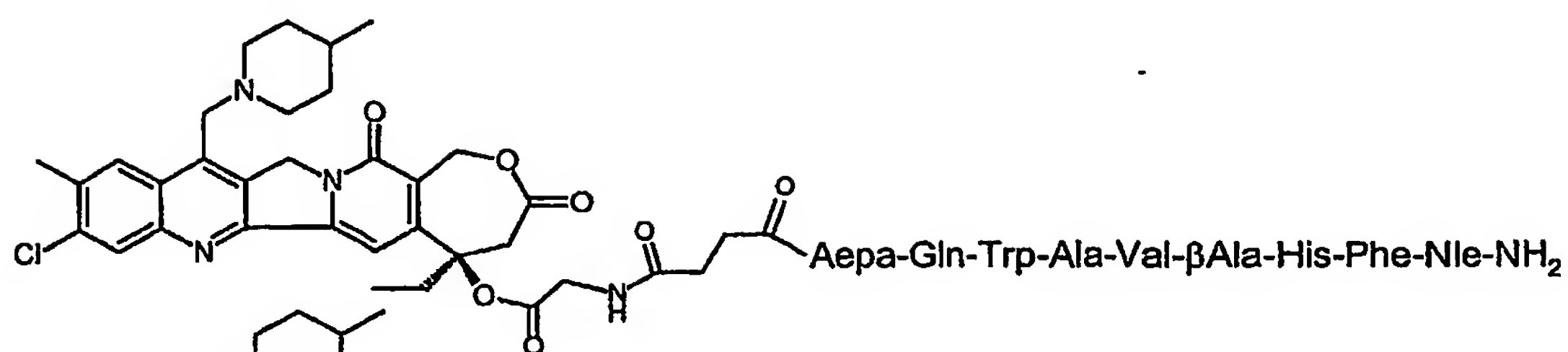


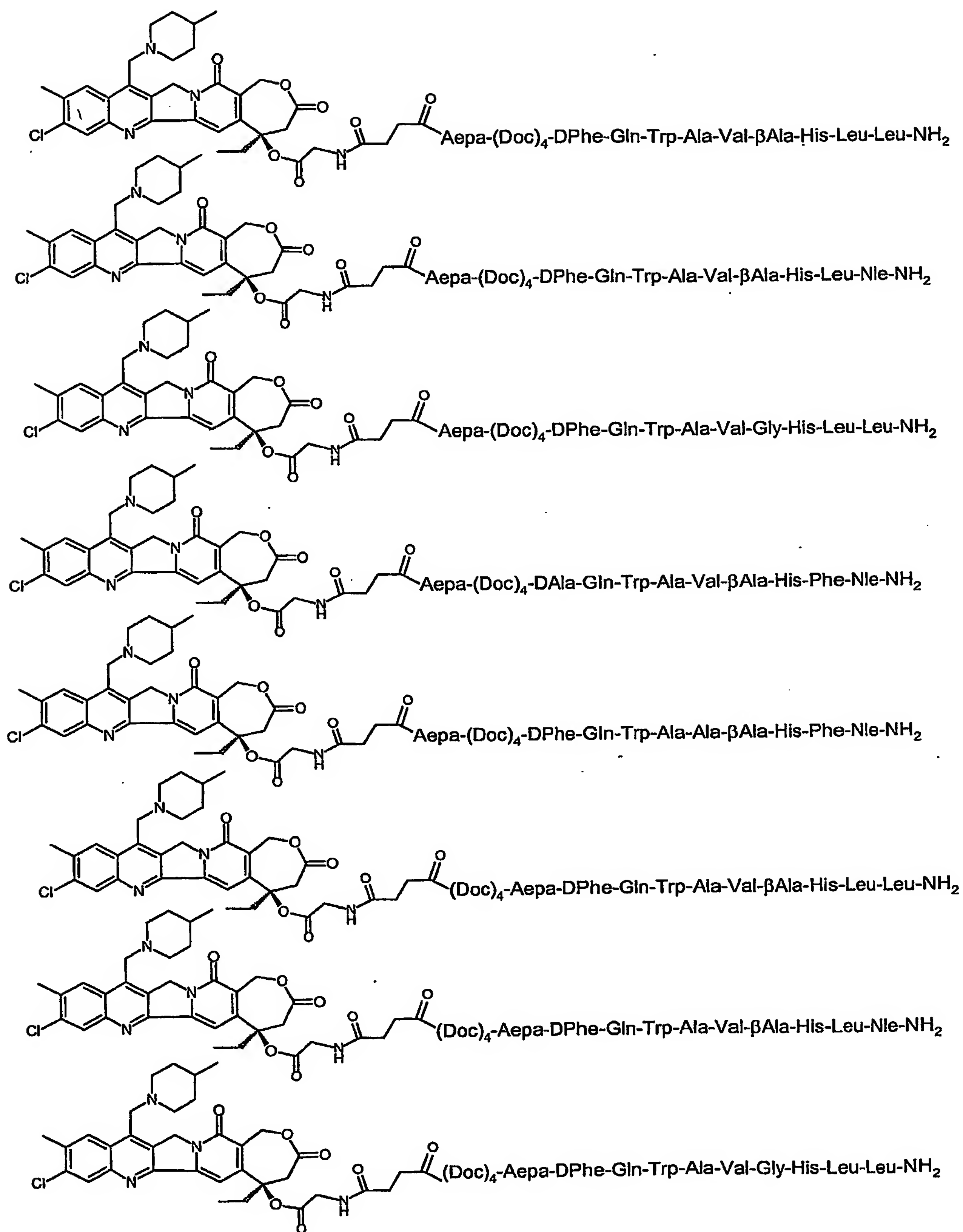


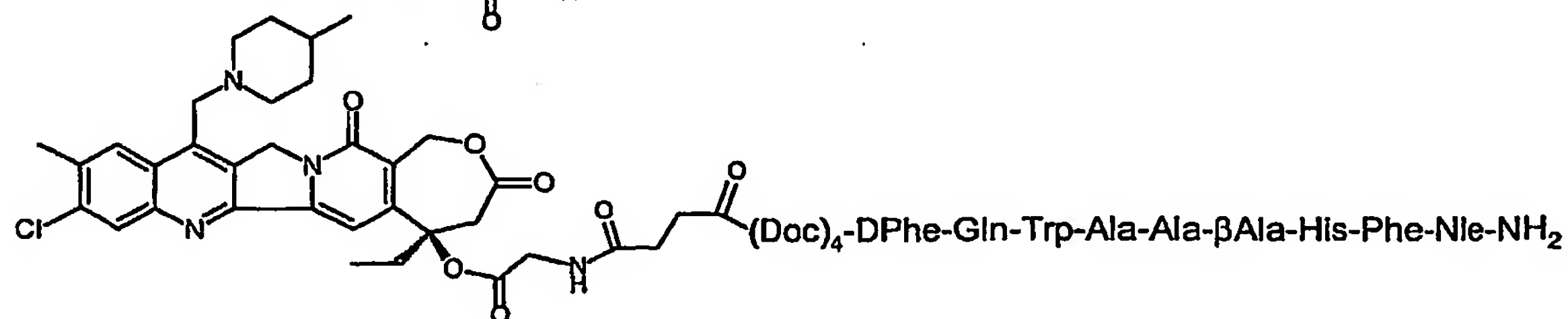
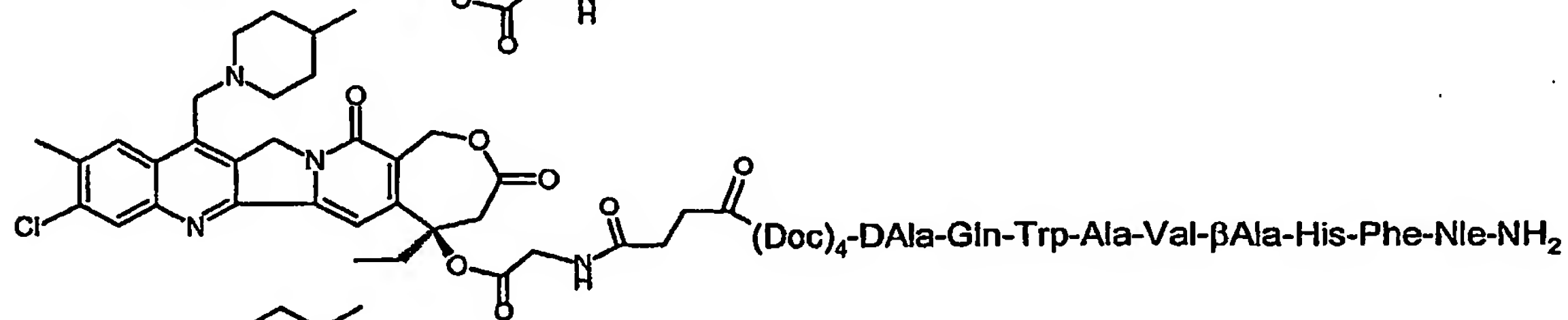
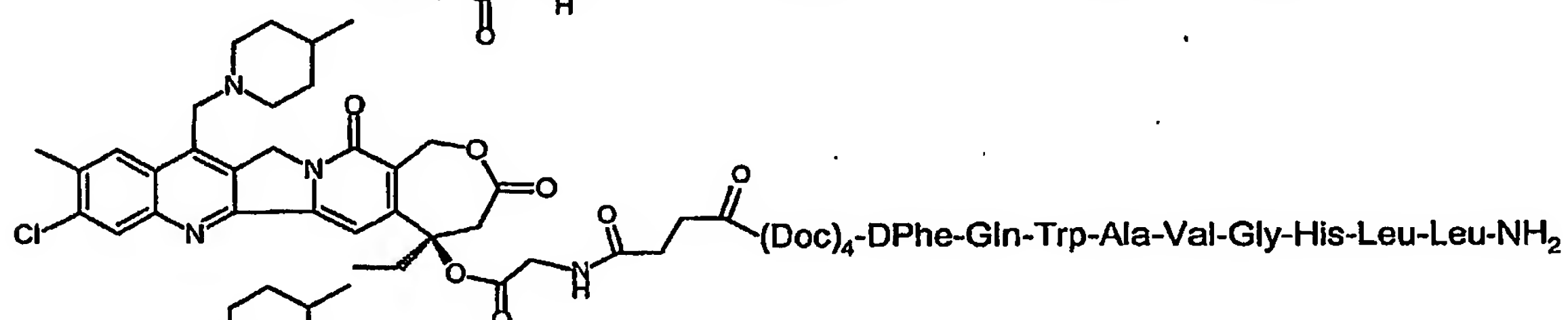
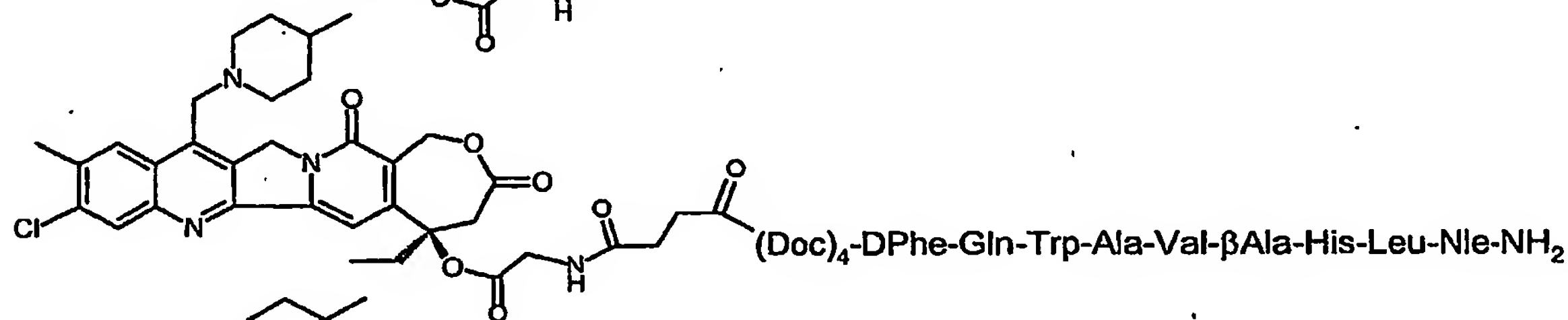
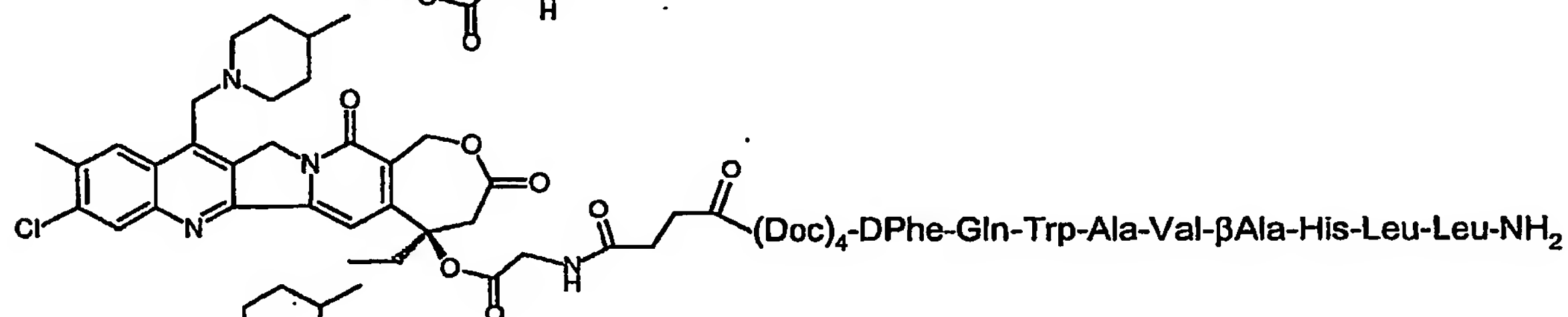
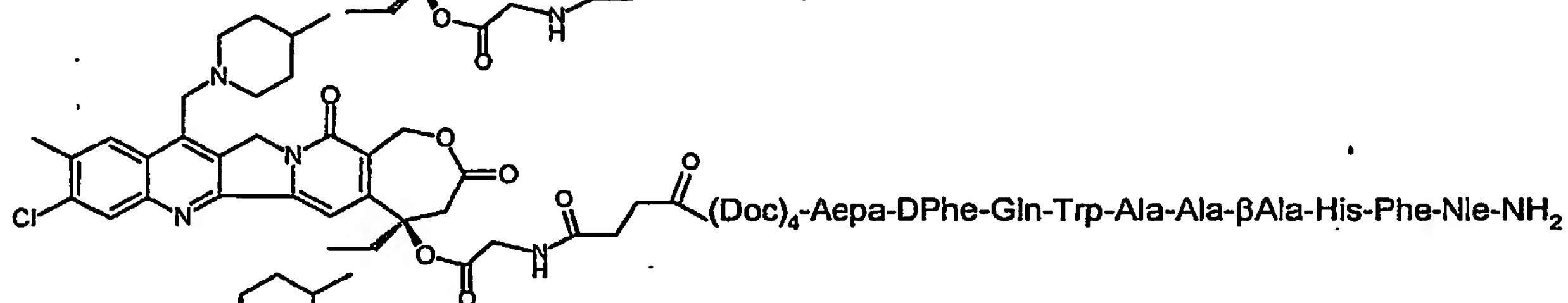
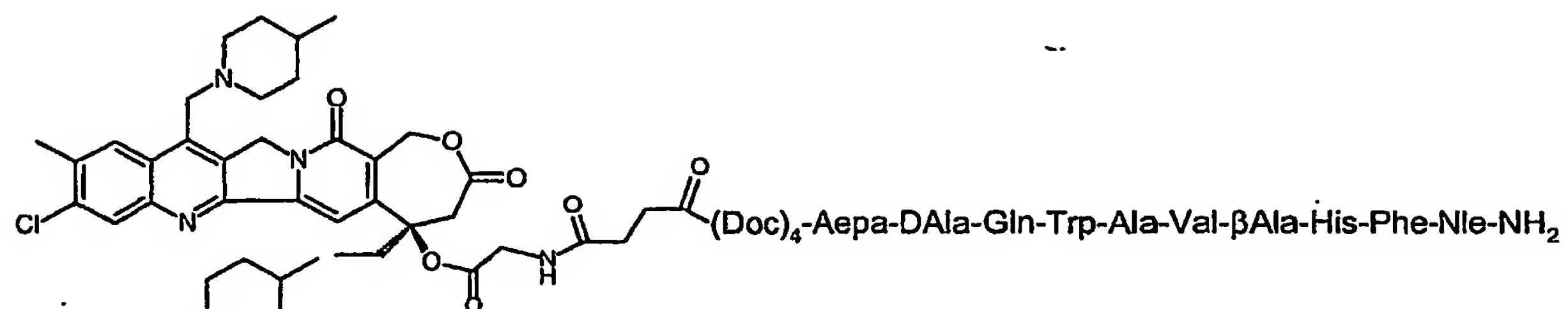


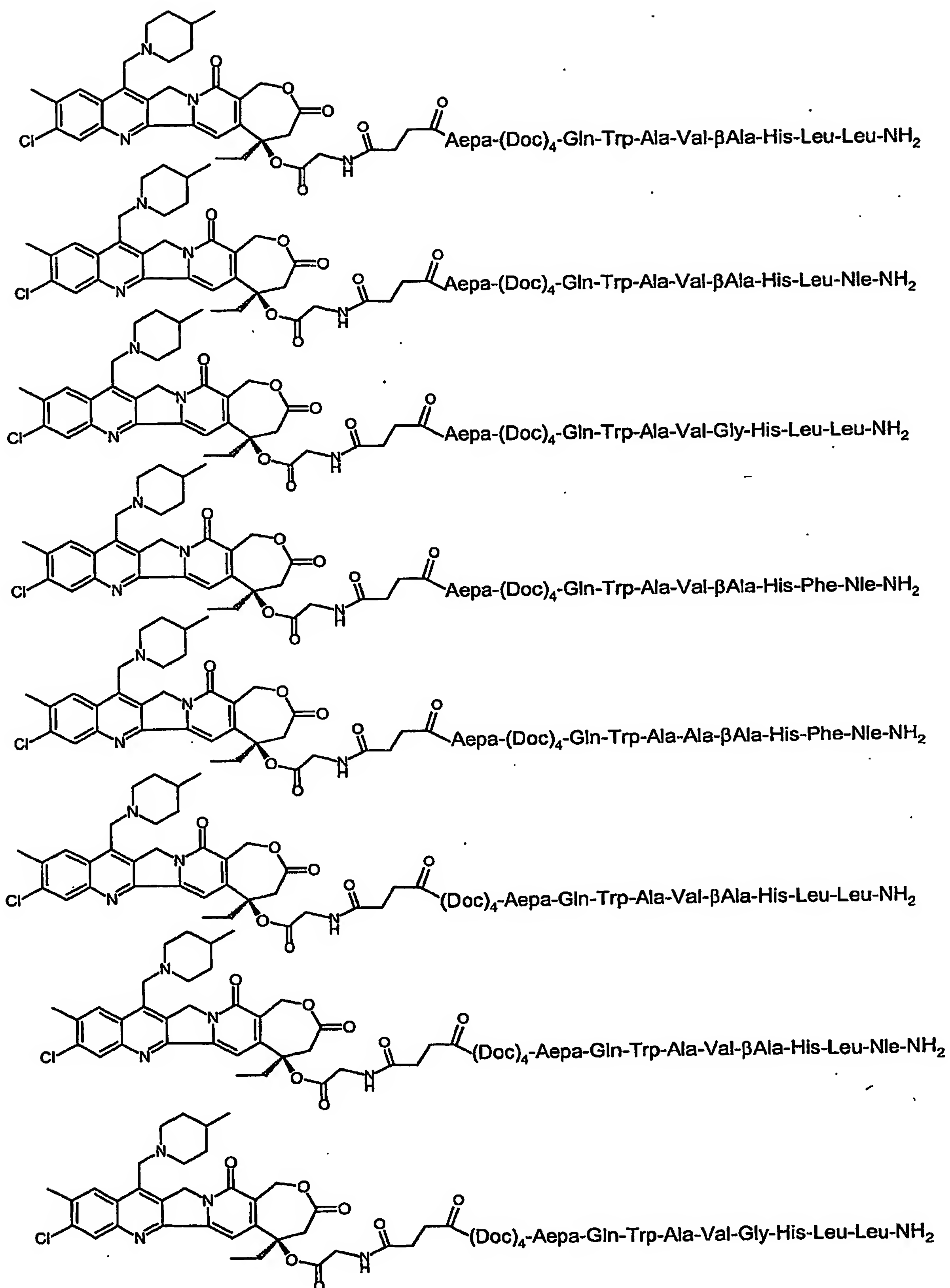


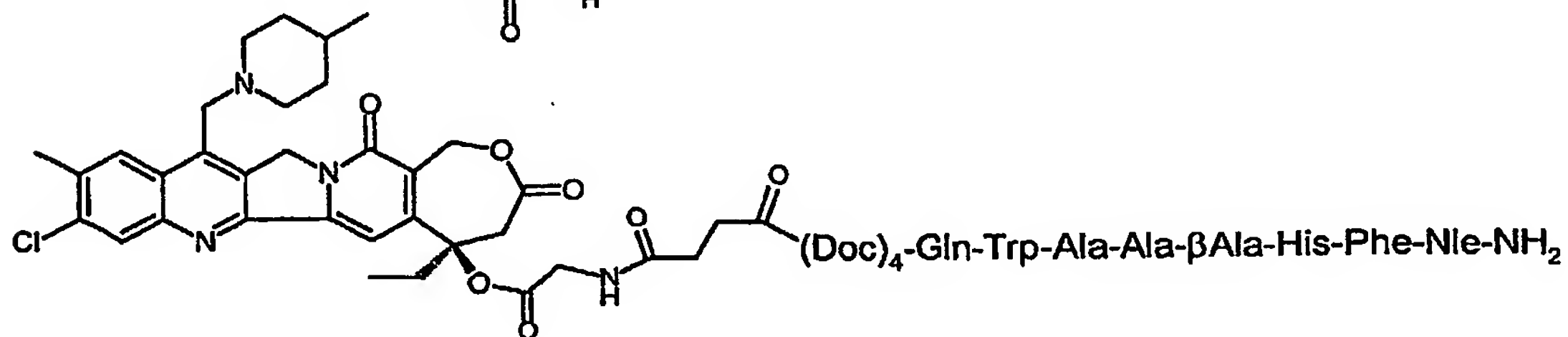
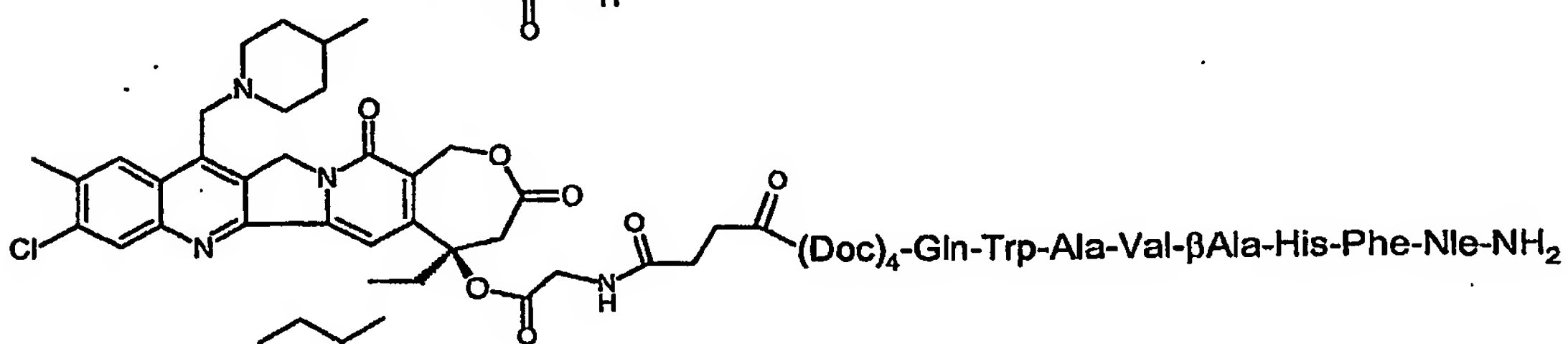
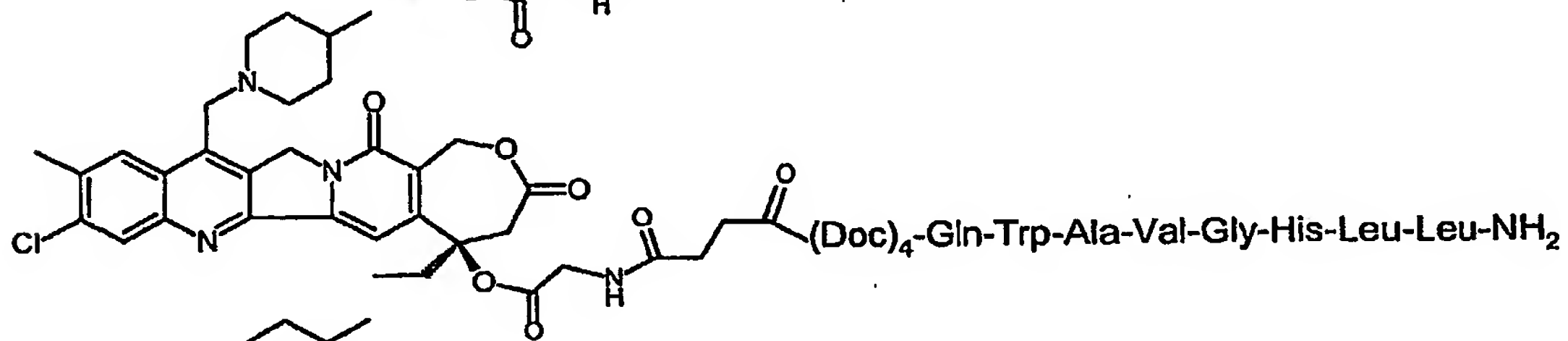
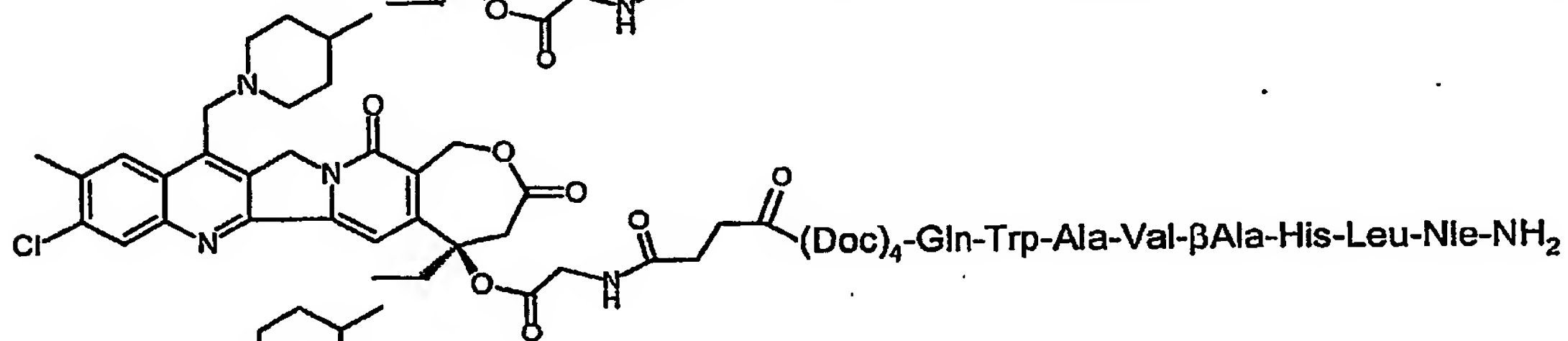
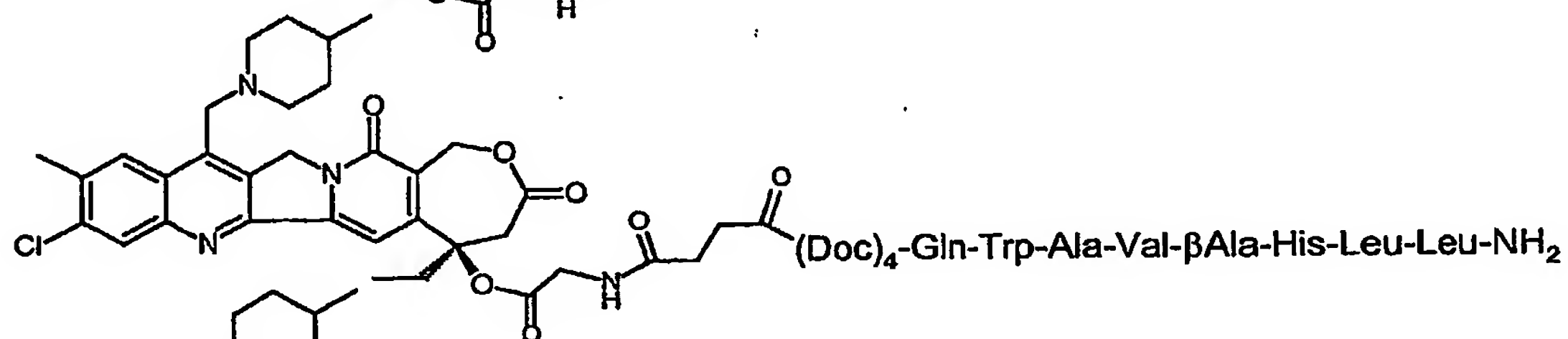
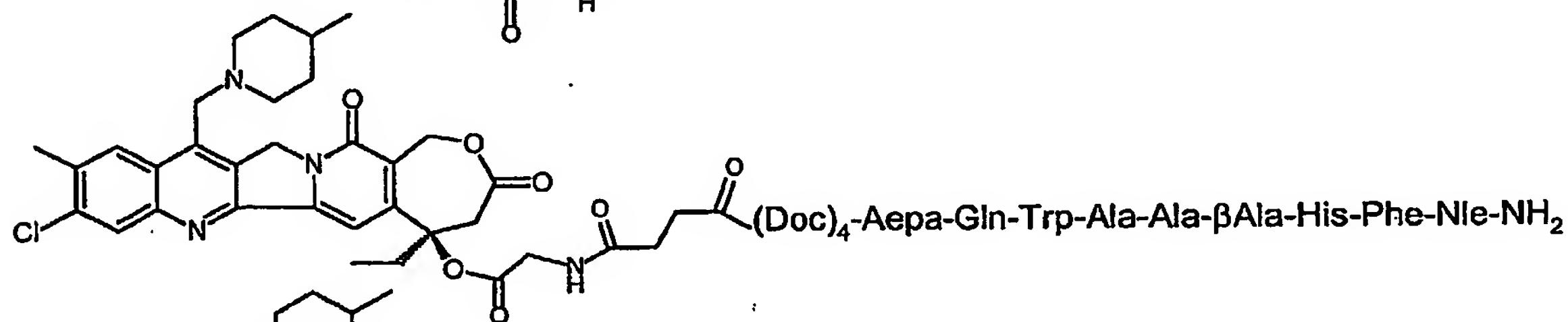
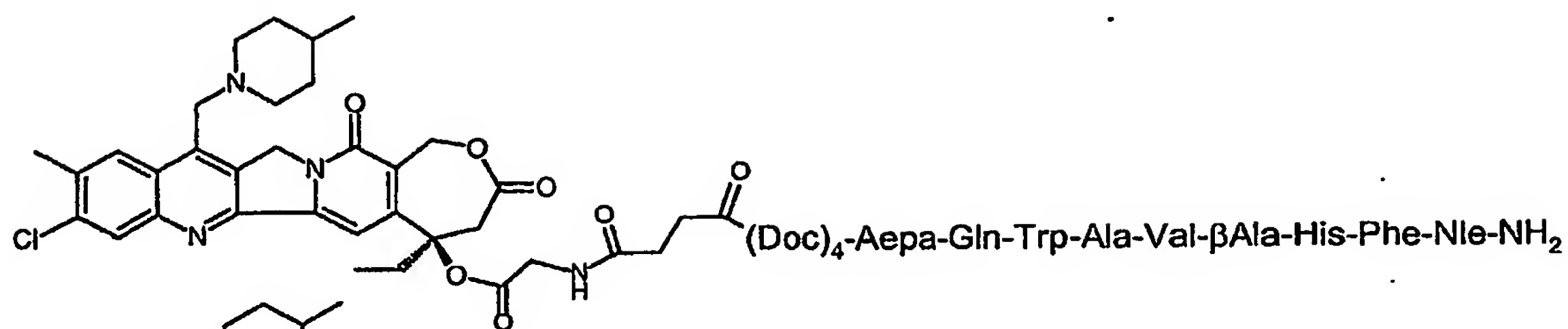


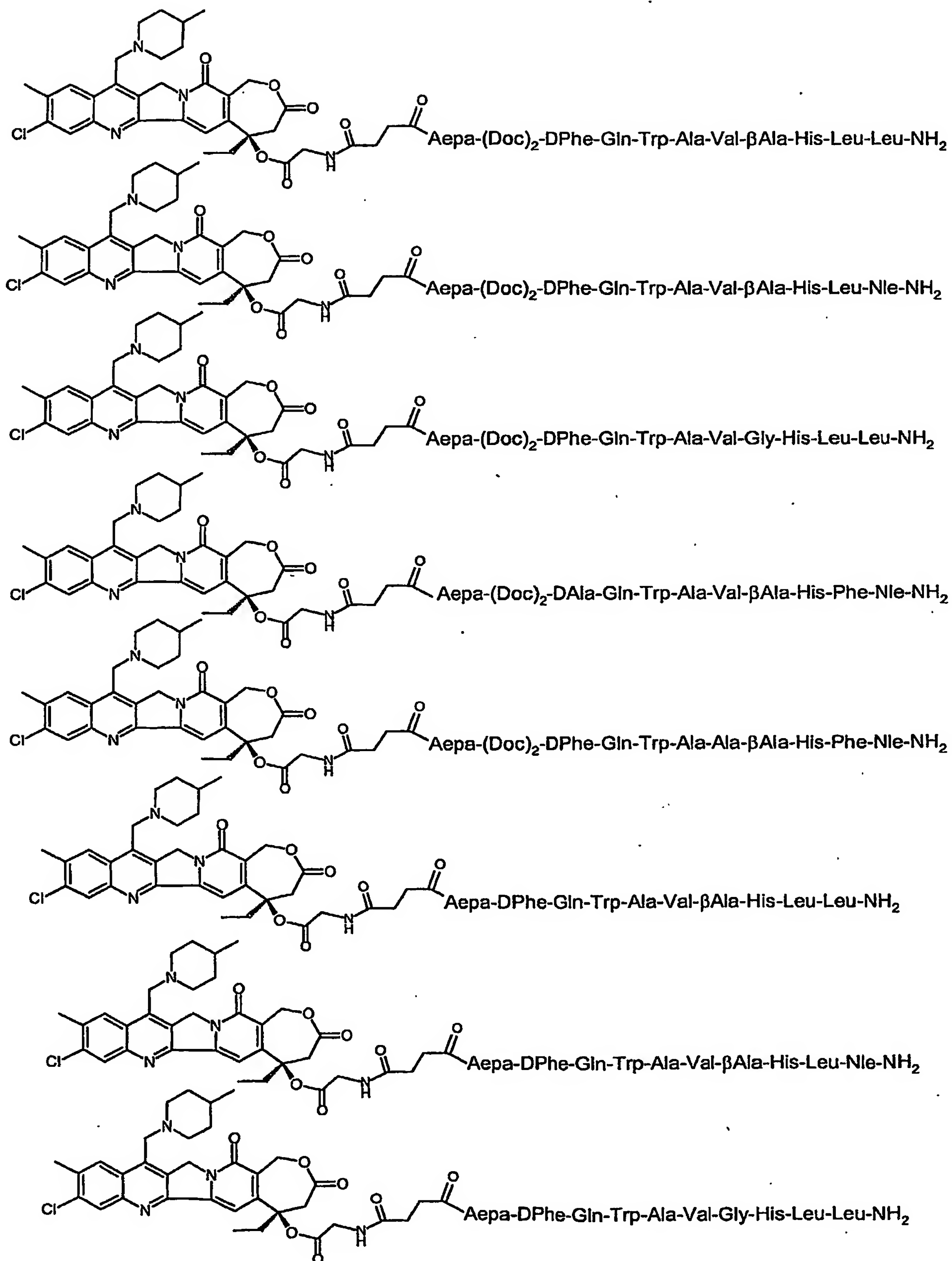




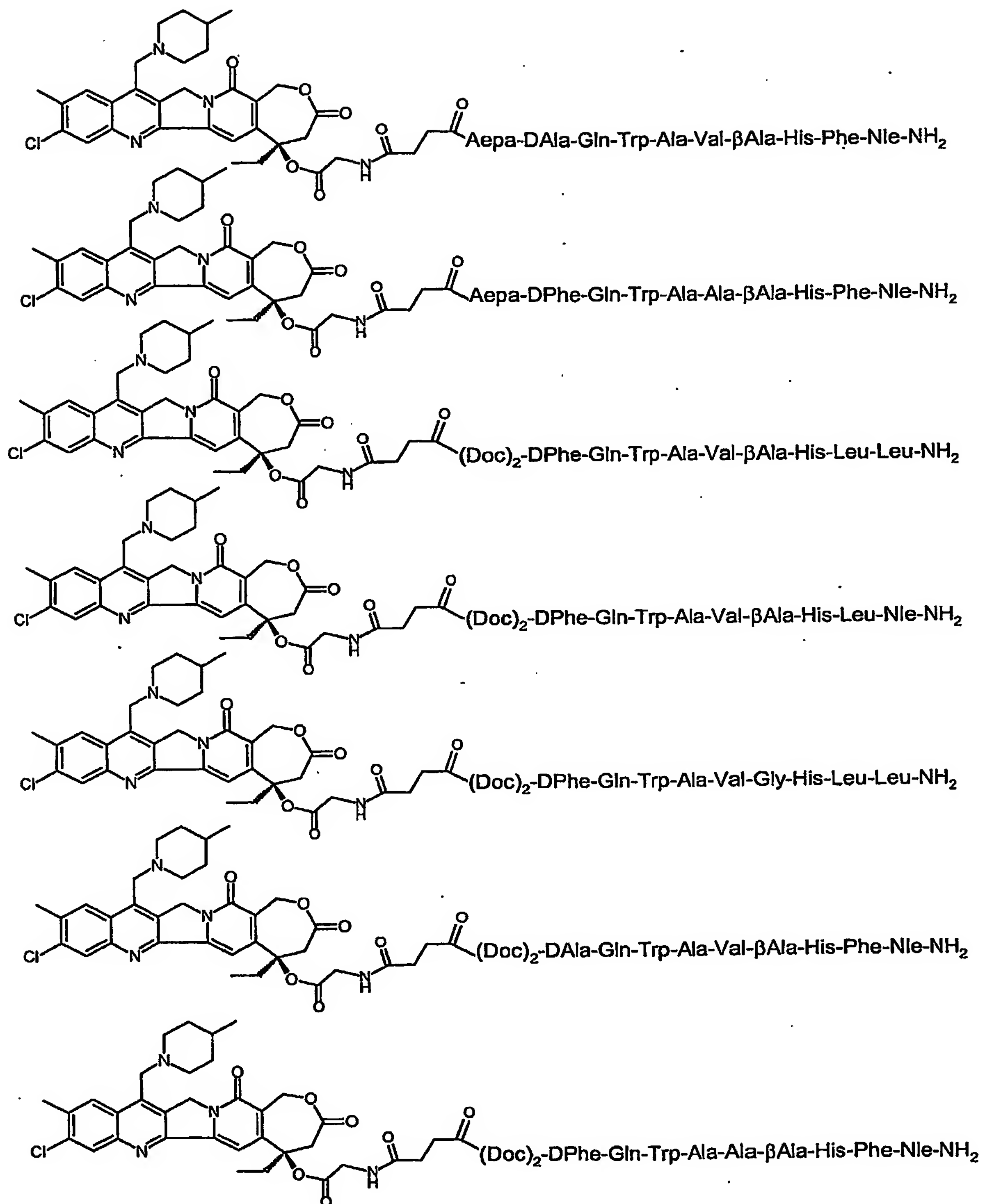


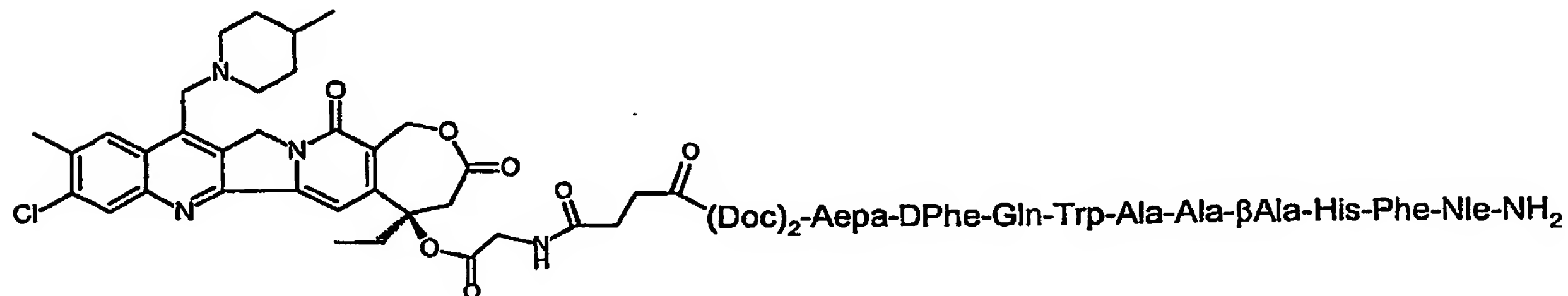
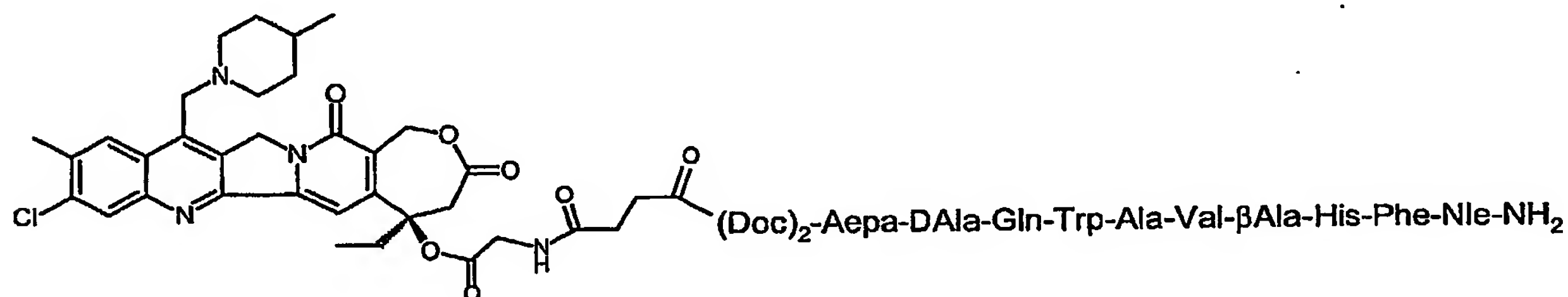
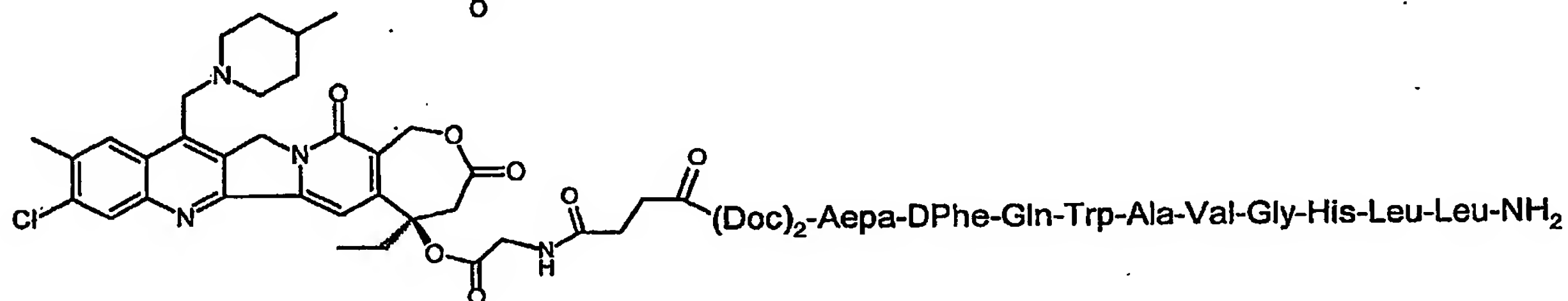
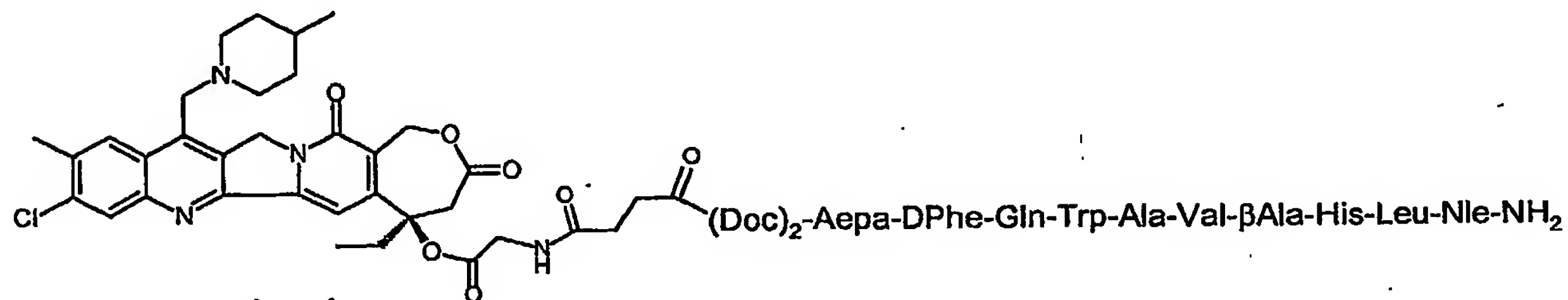
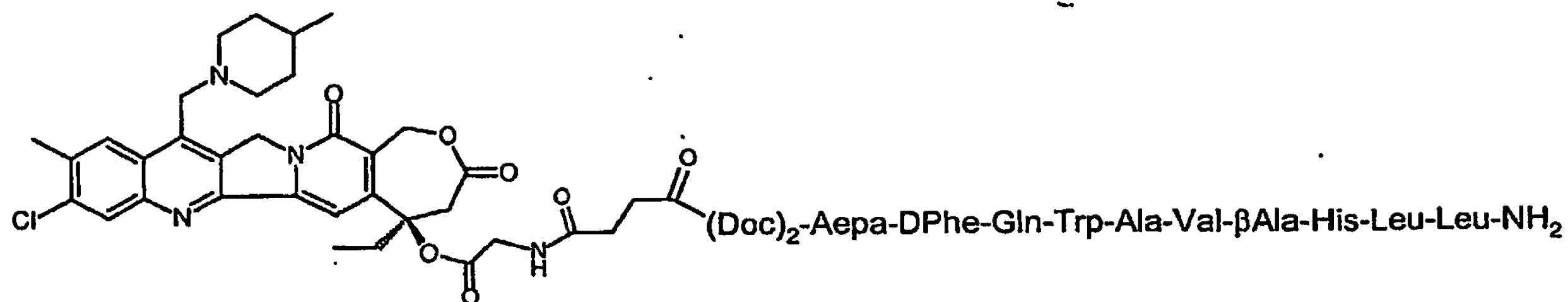


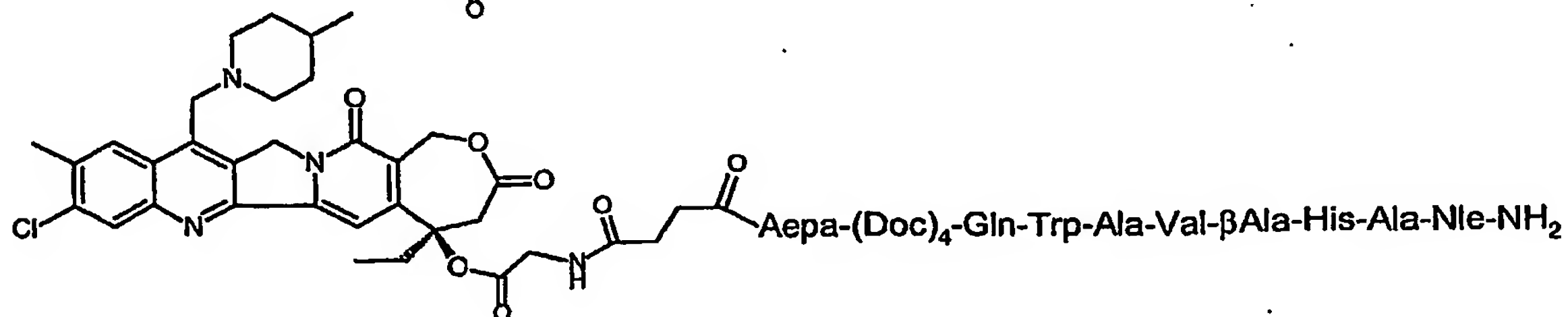
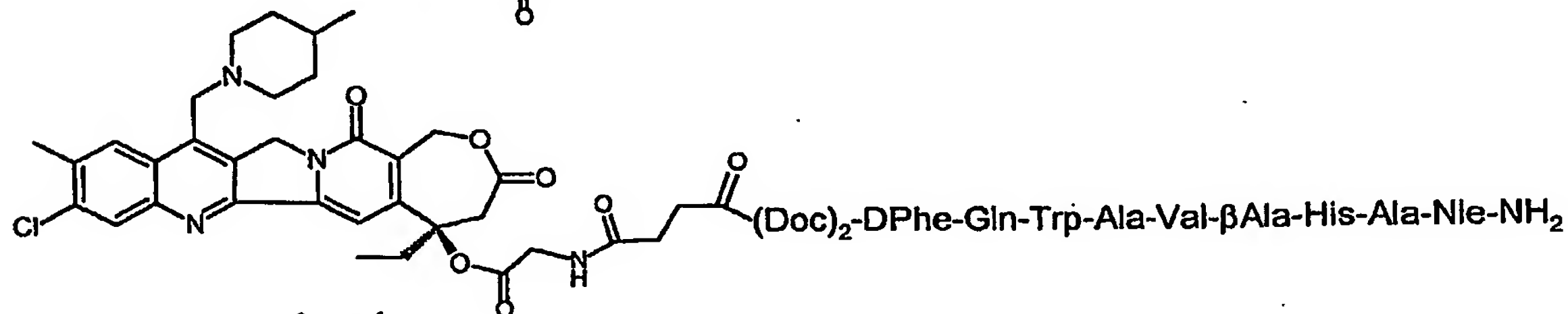
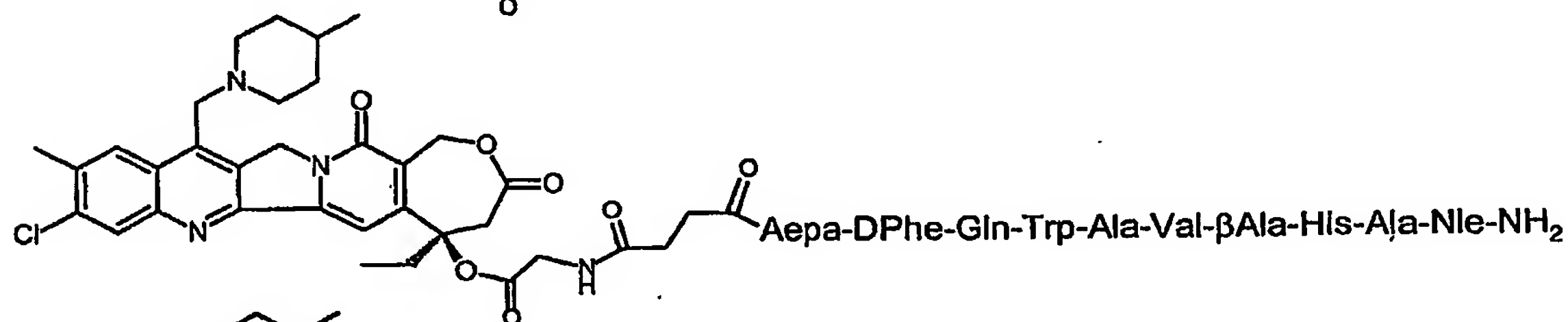
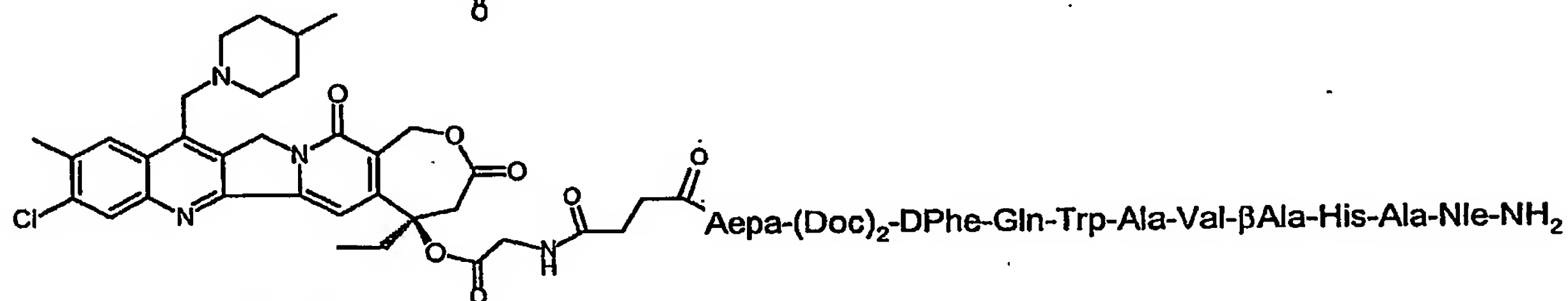
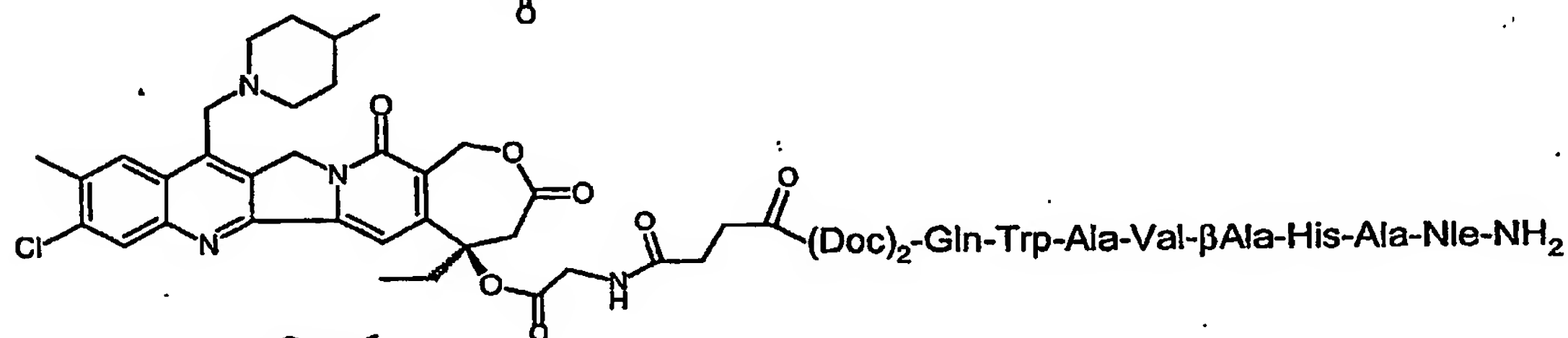
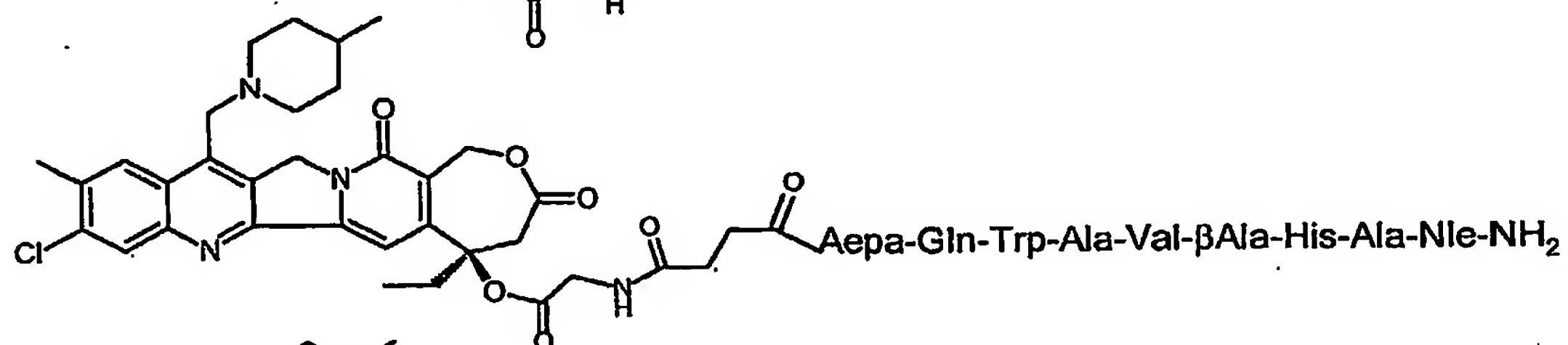
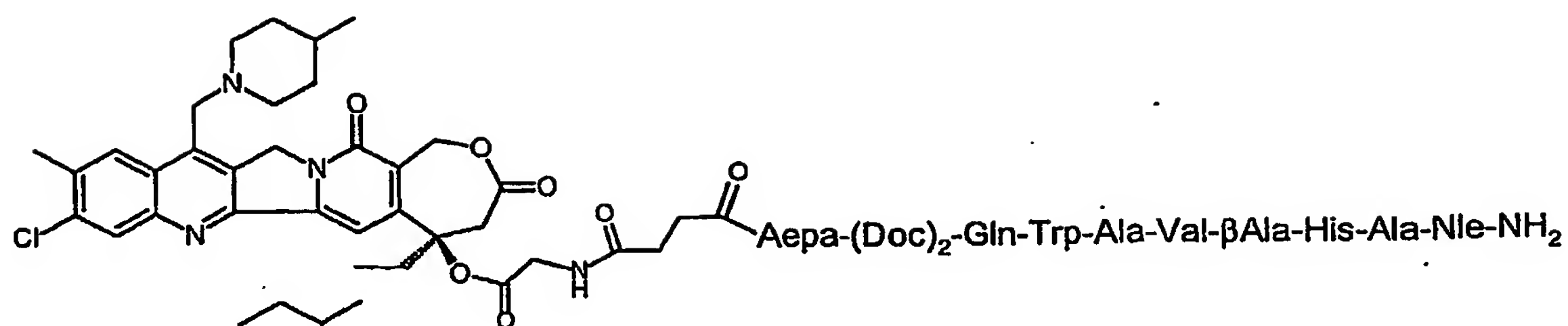


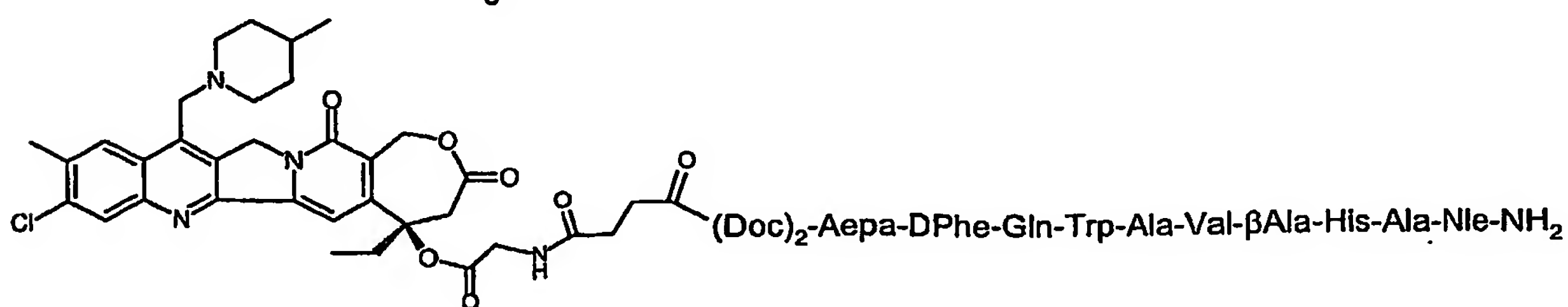
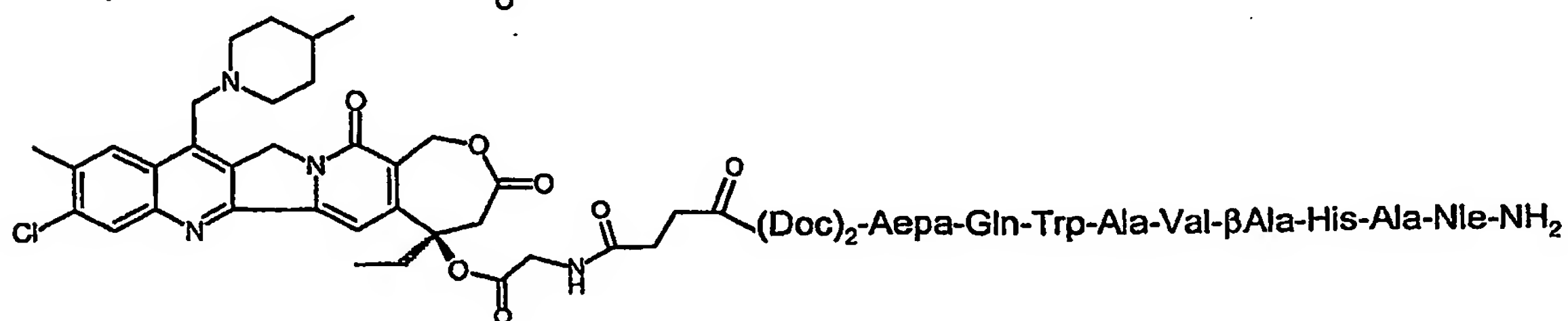
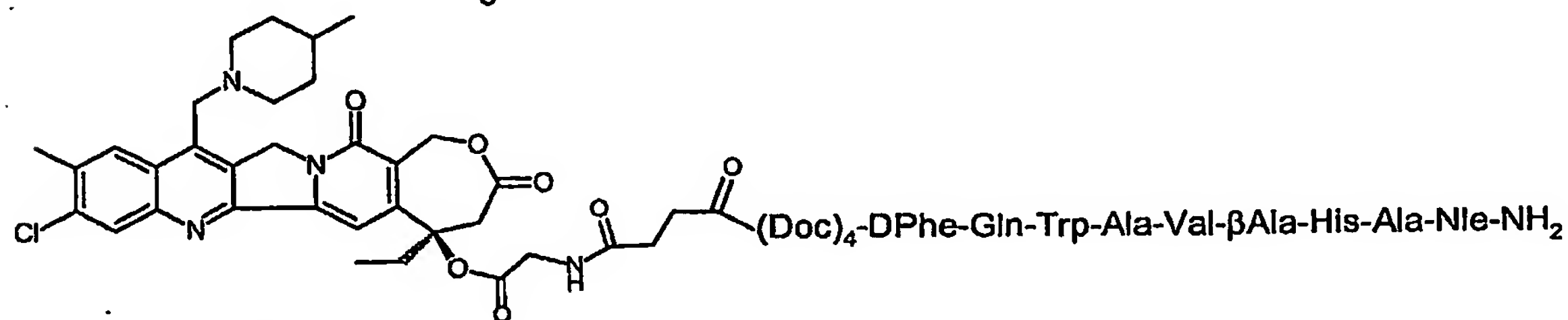
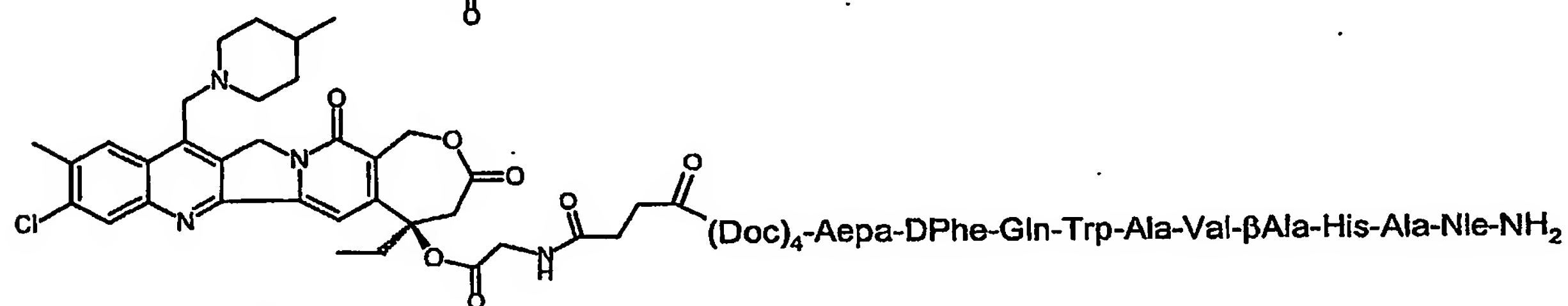
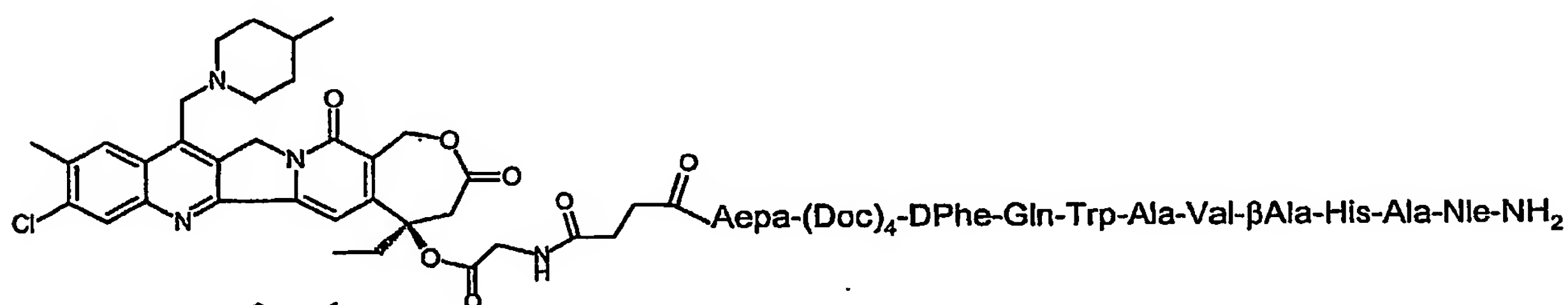
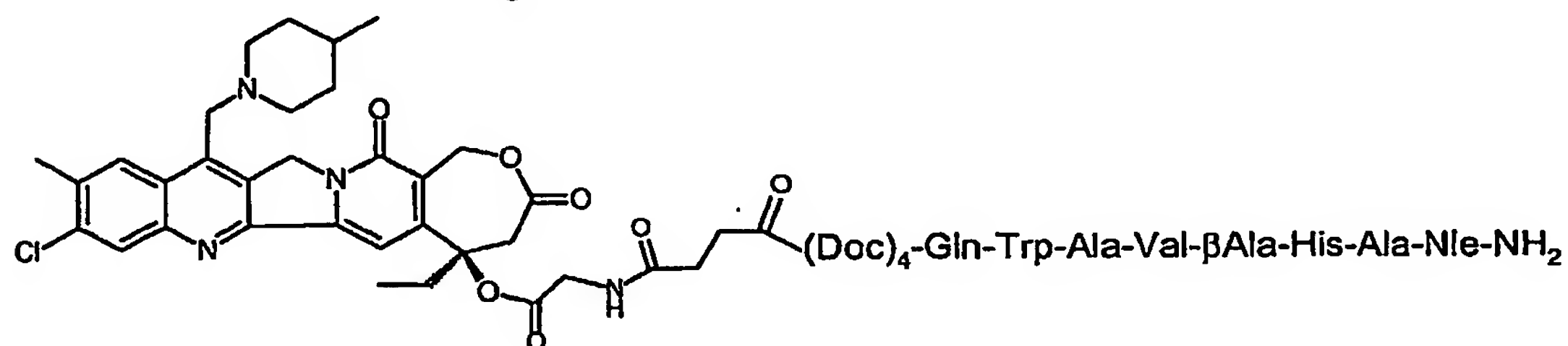
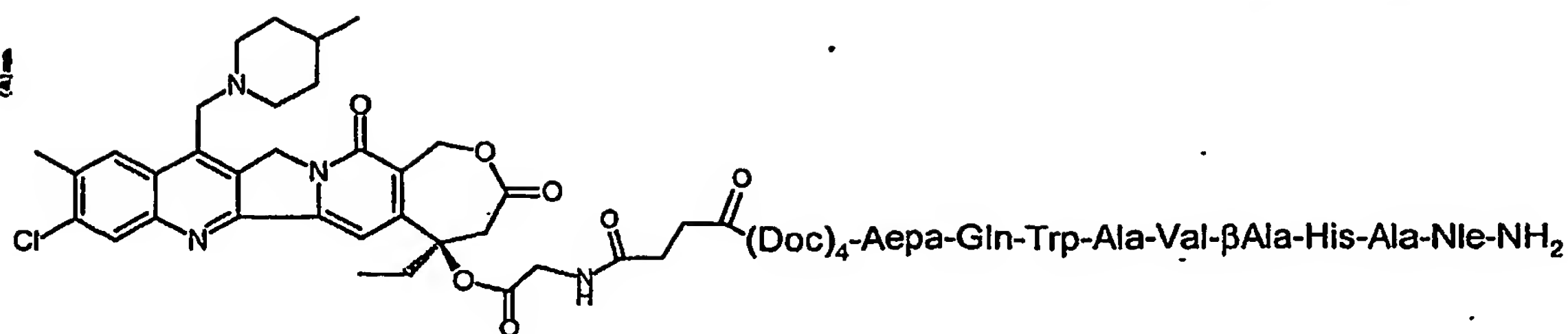


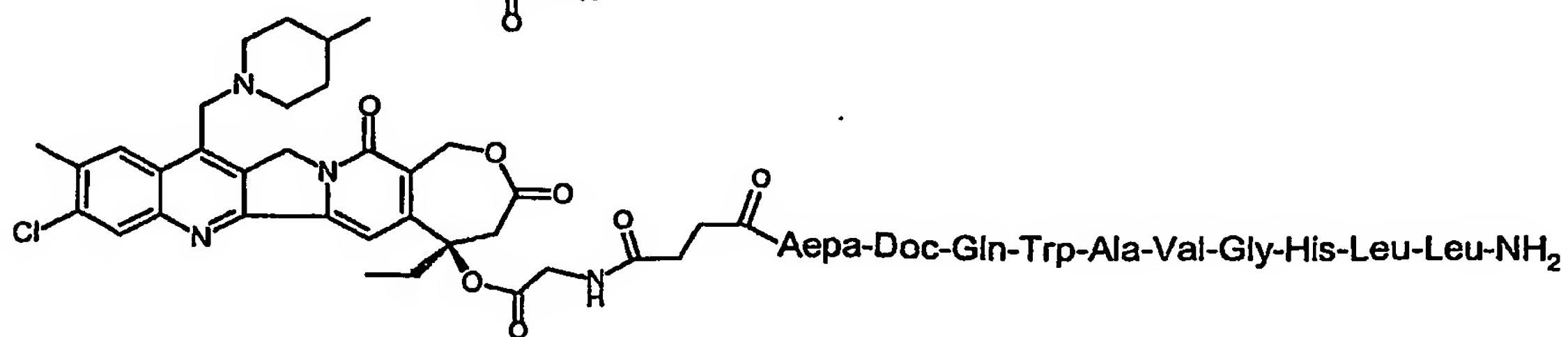
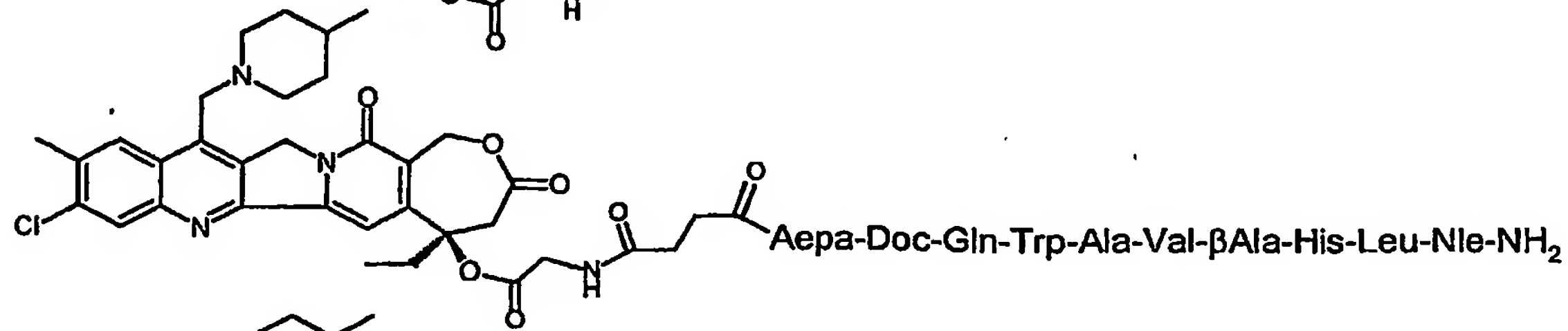
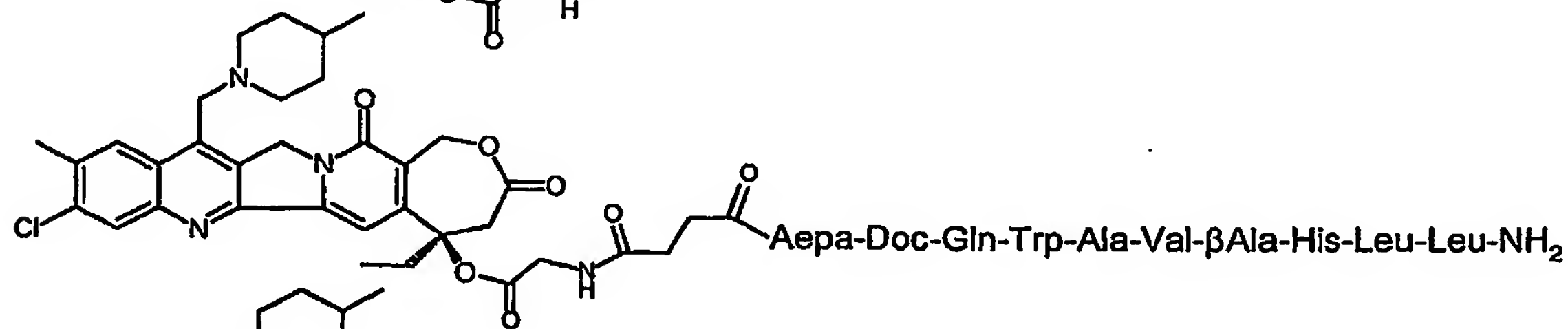
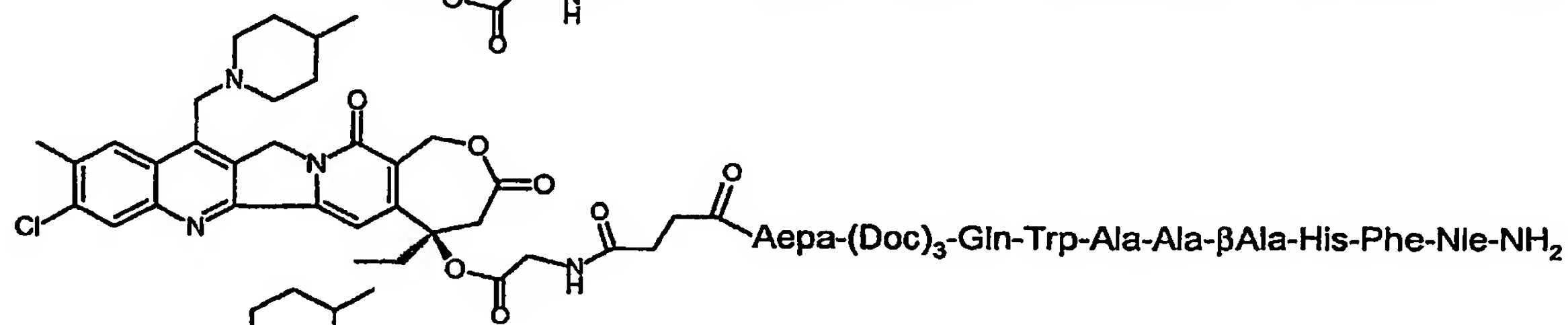
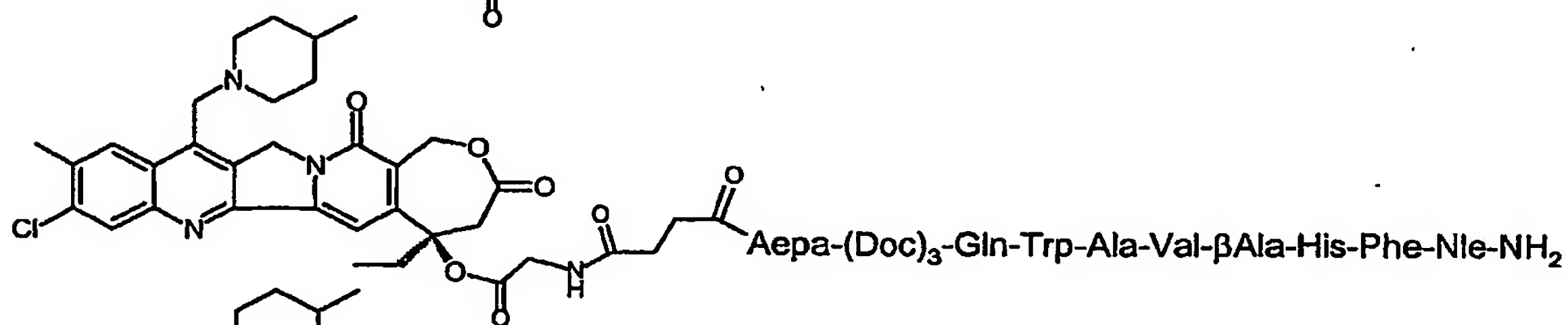
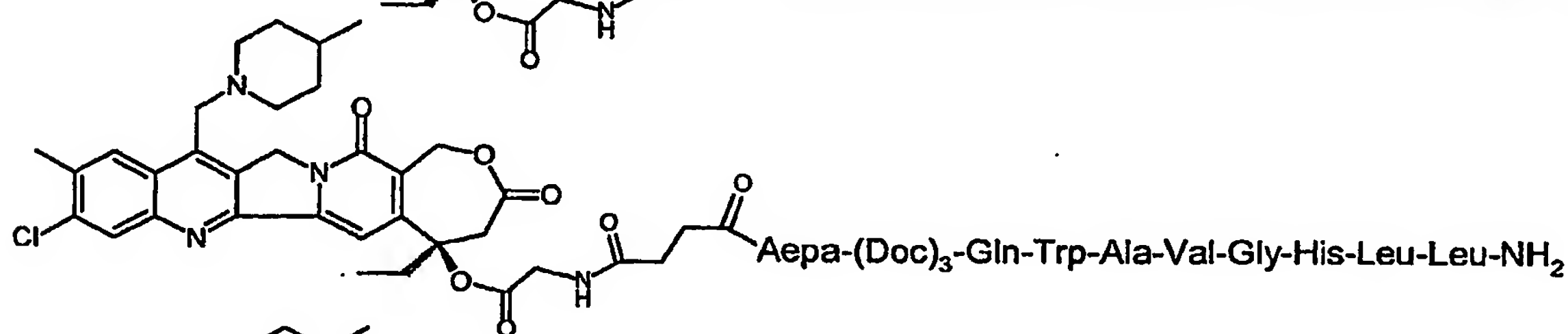
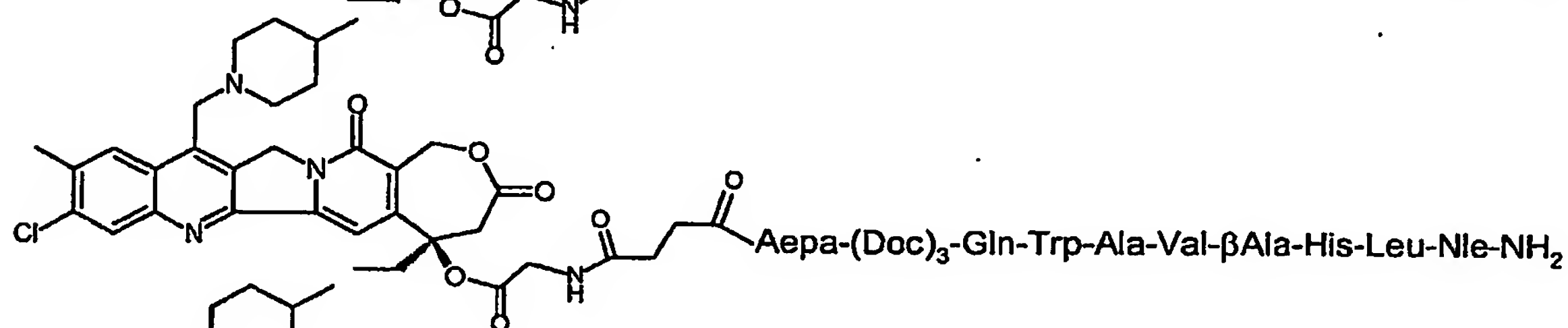
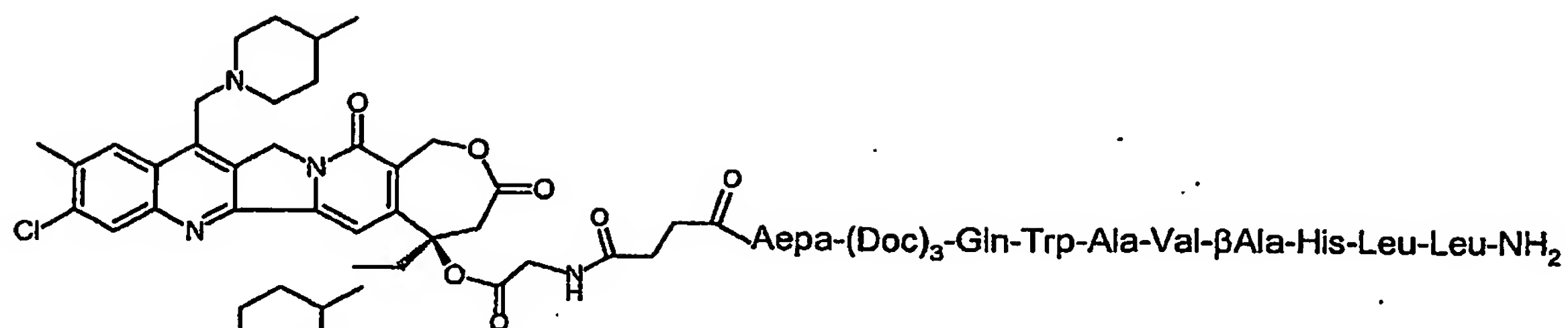
Appendix C

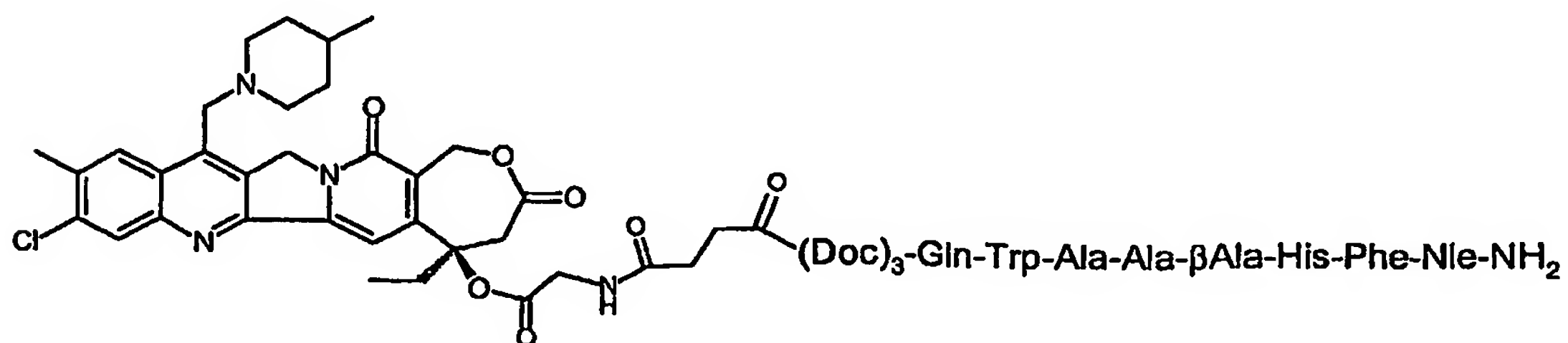
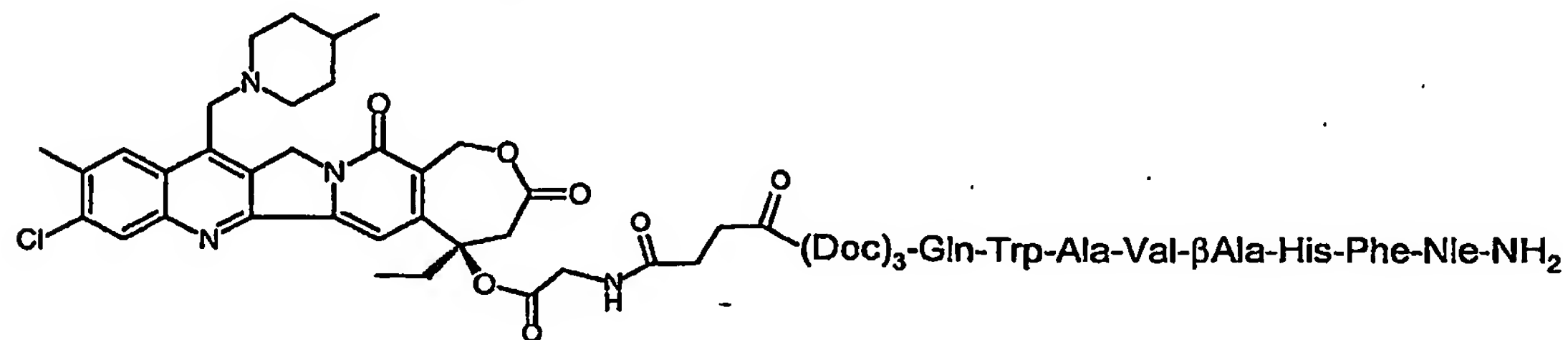
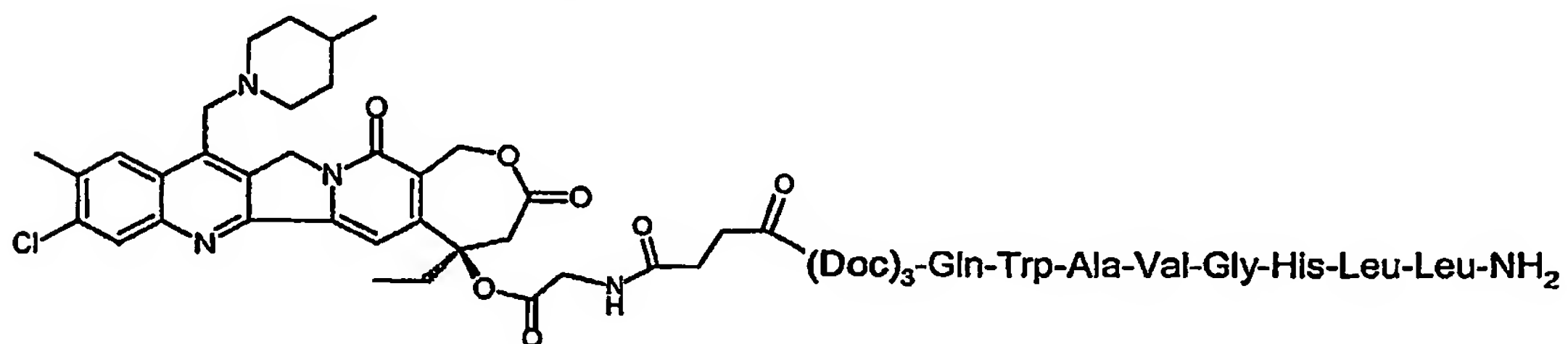
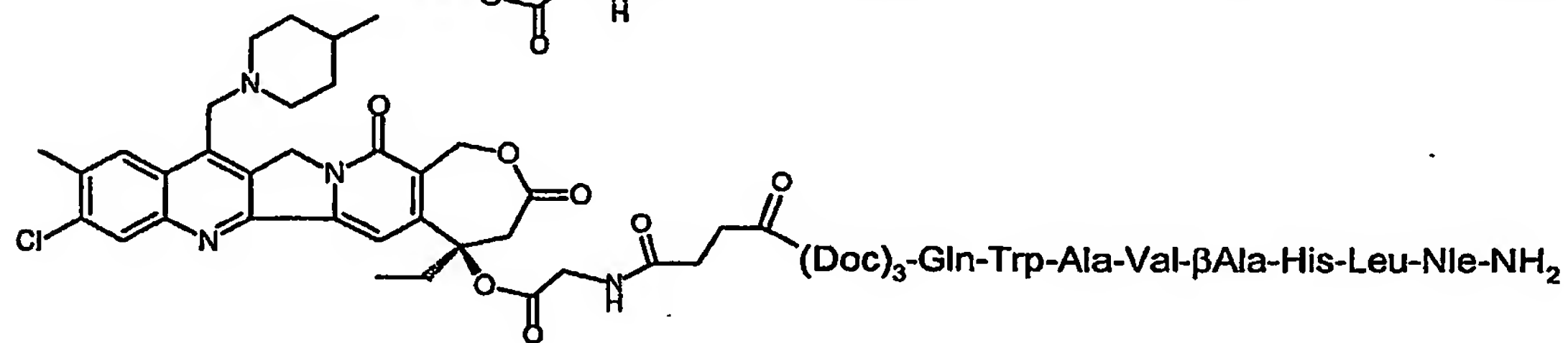
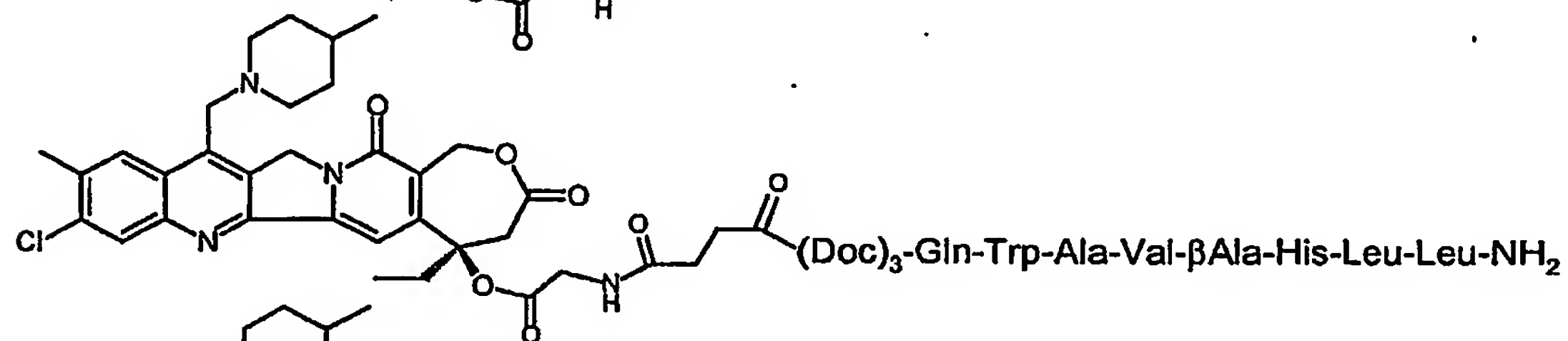
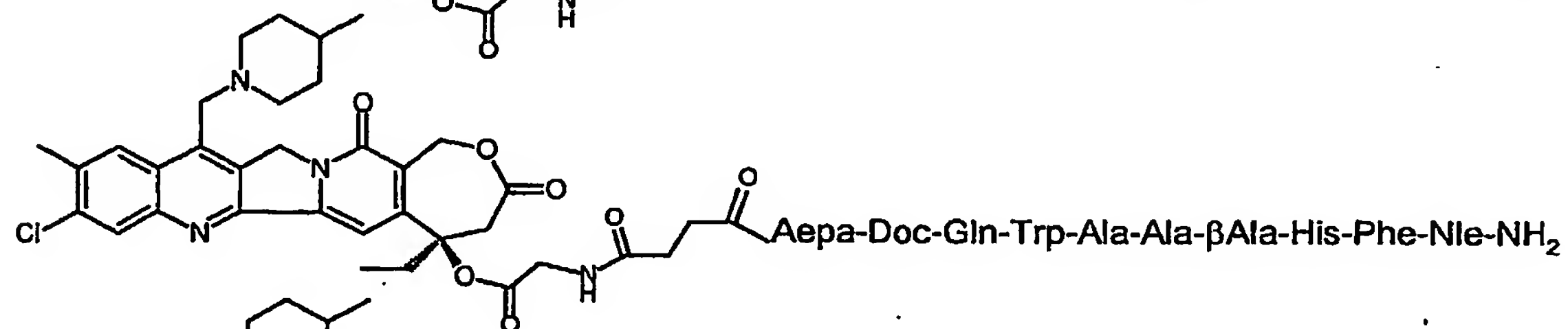
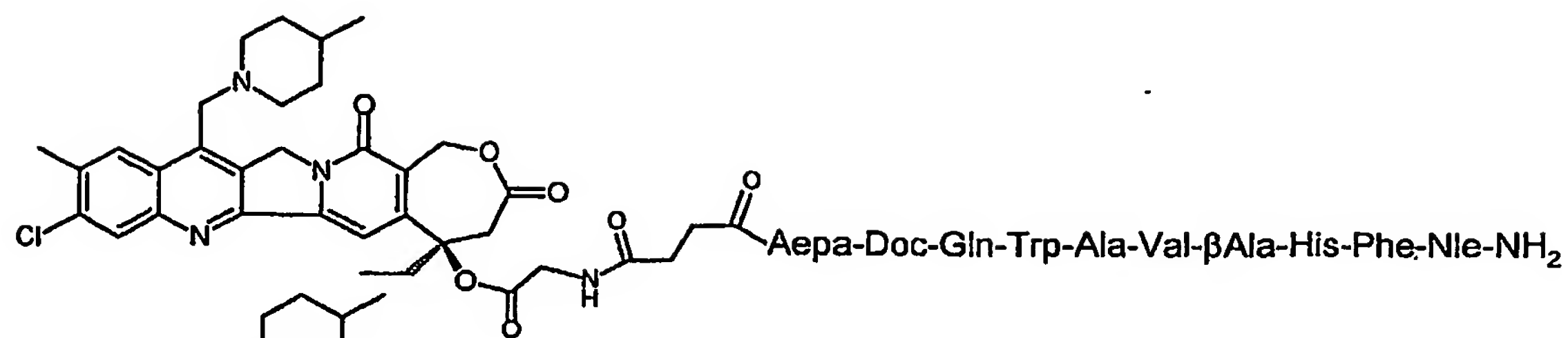


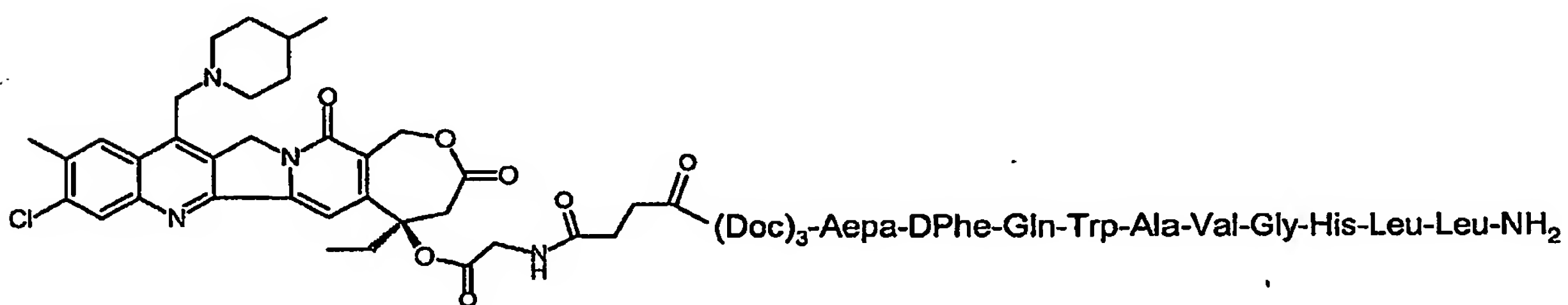
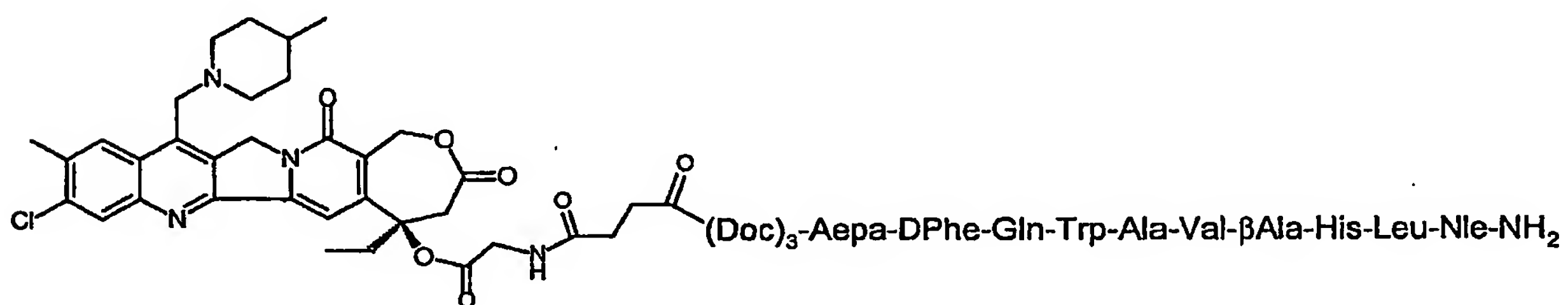
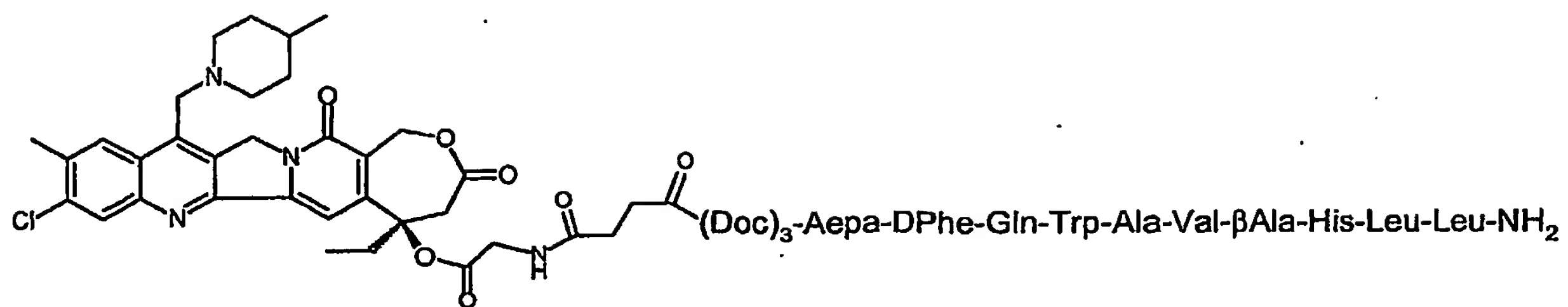




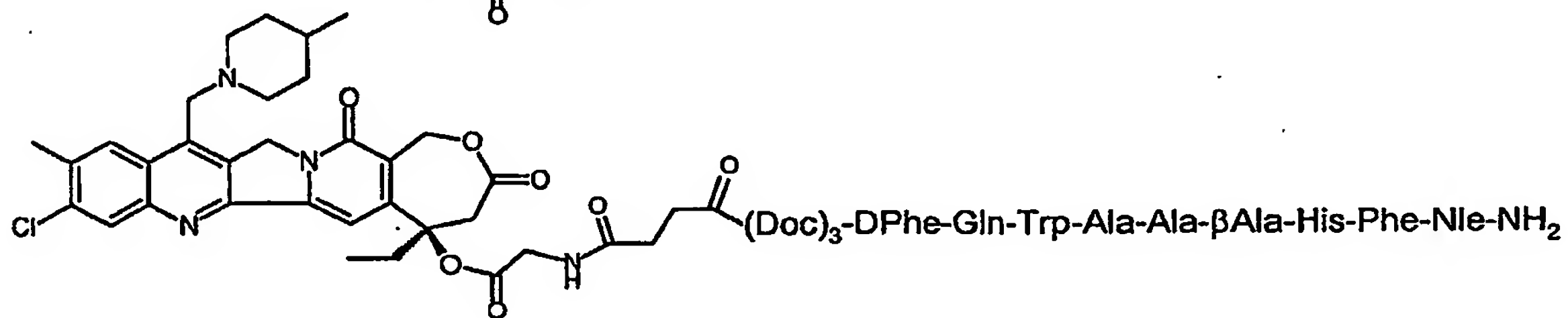
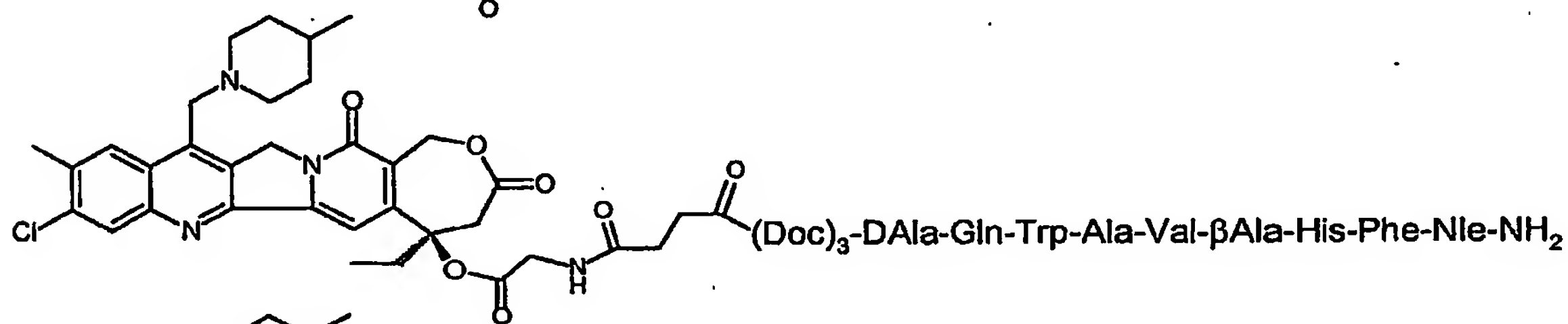
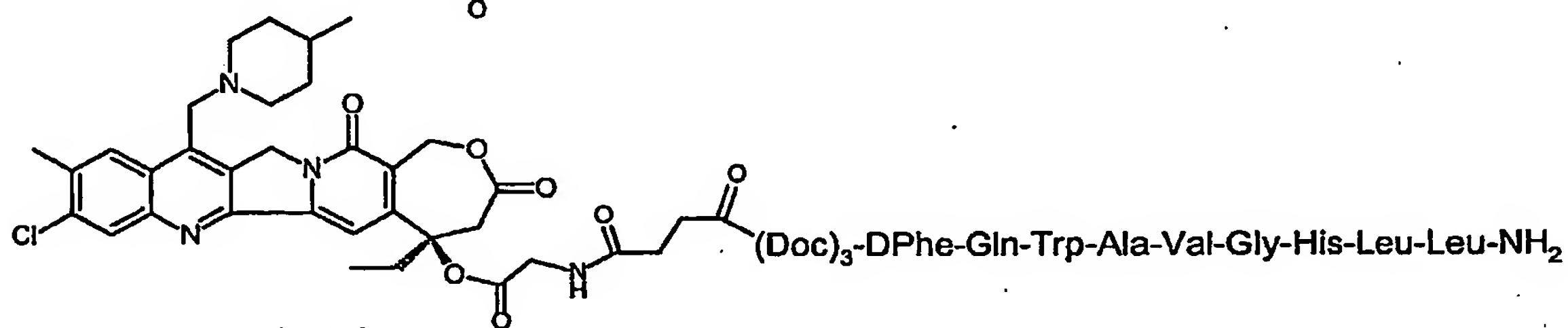
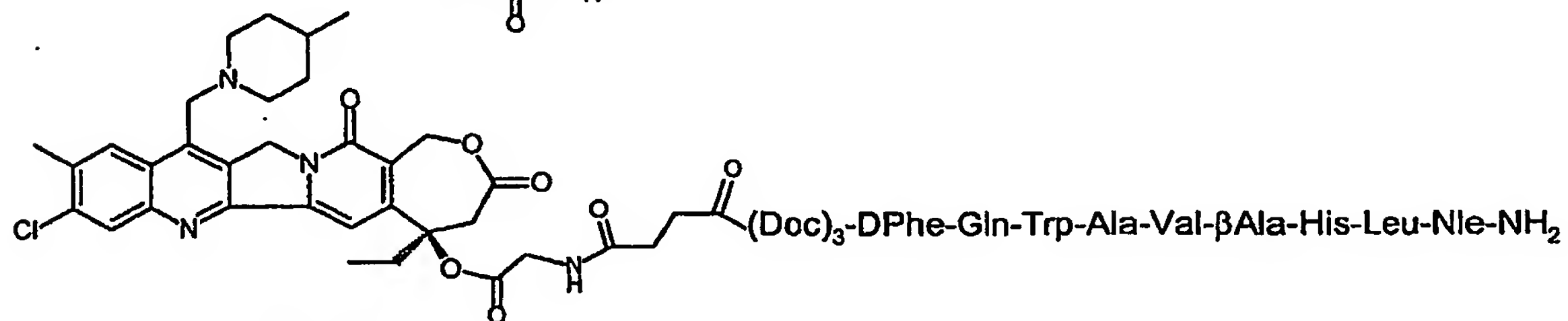
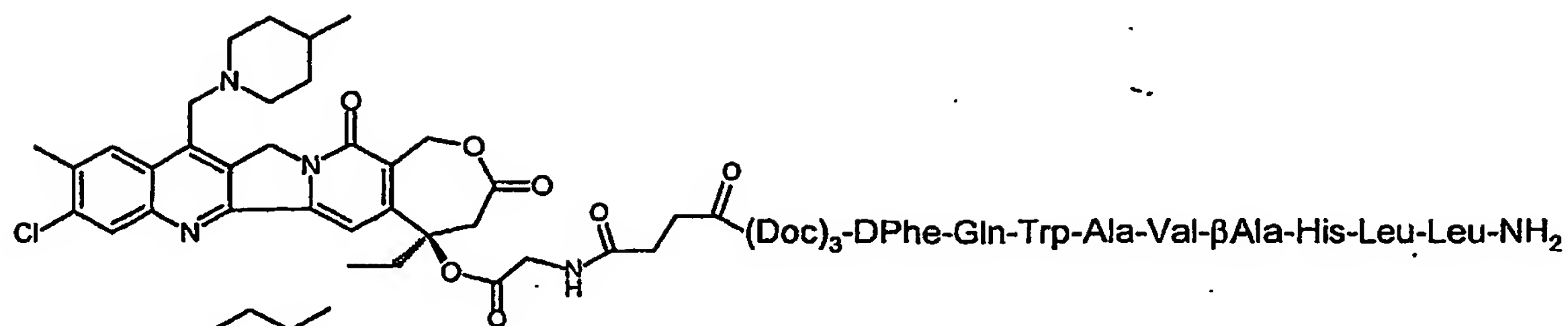


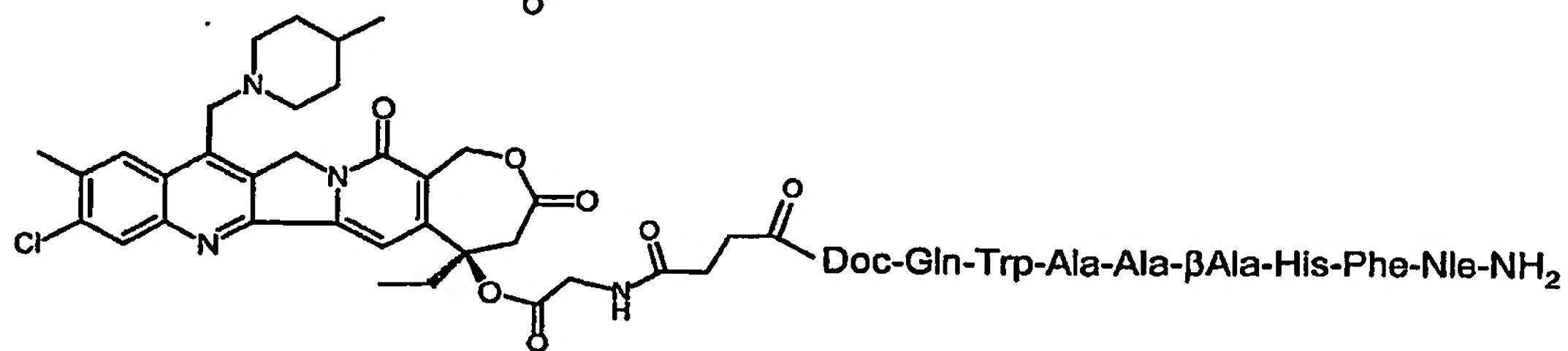
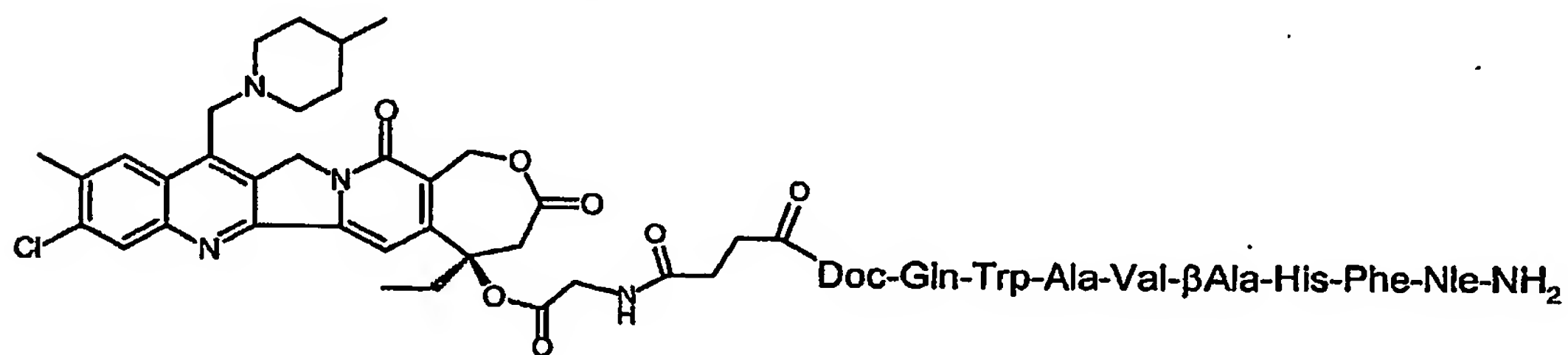
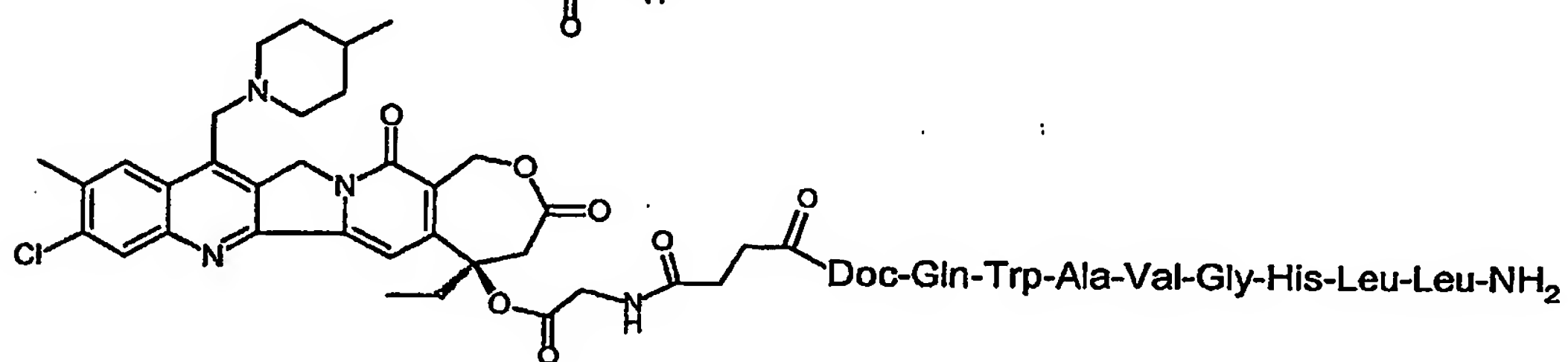
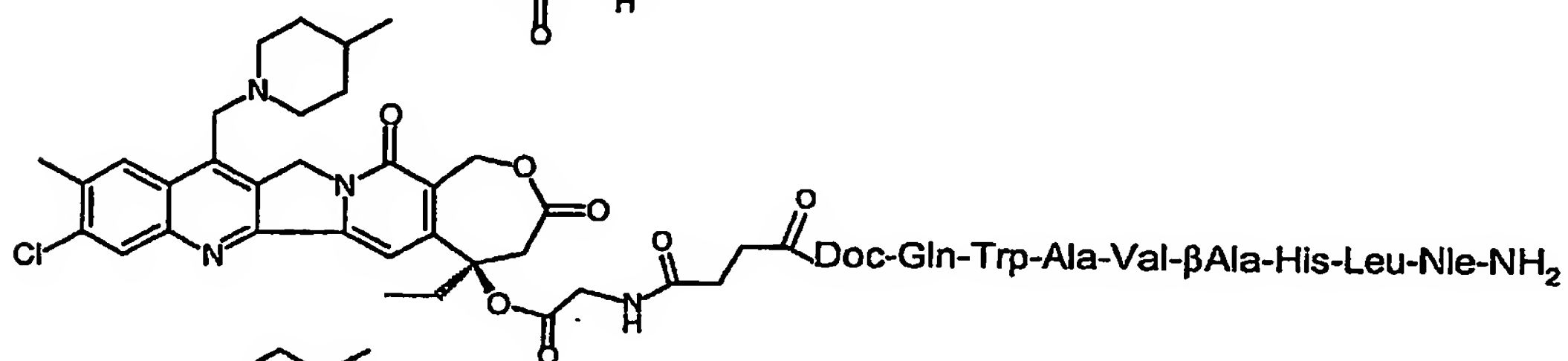
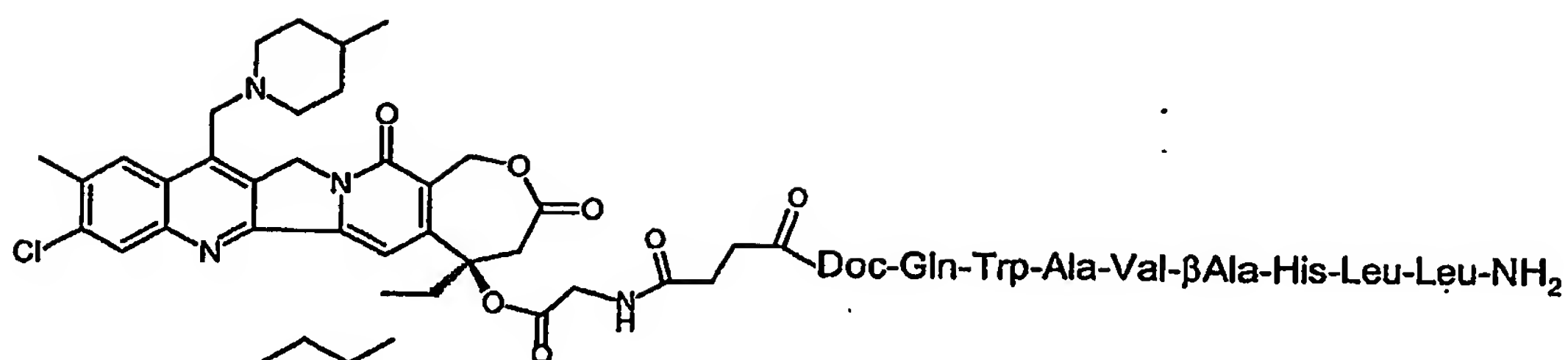


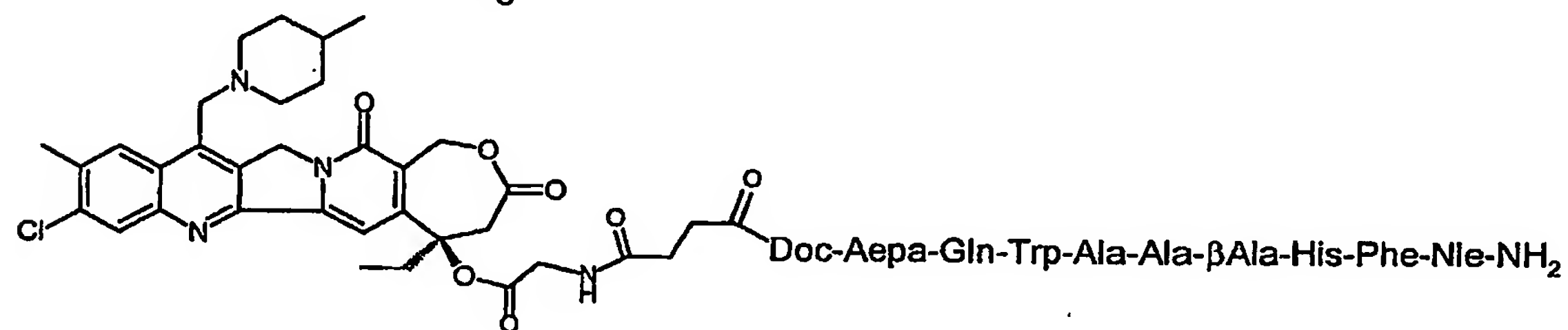
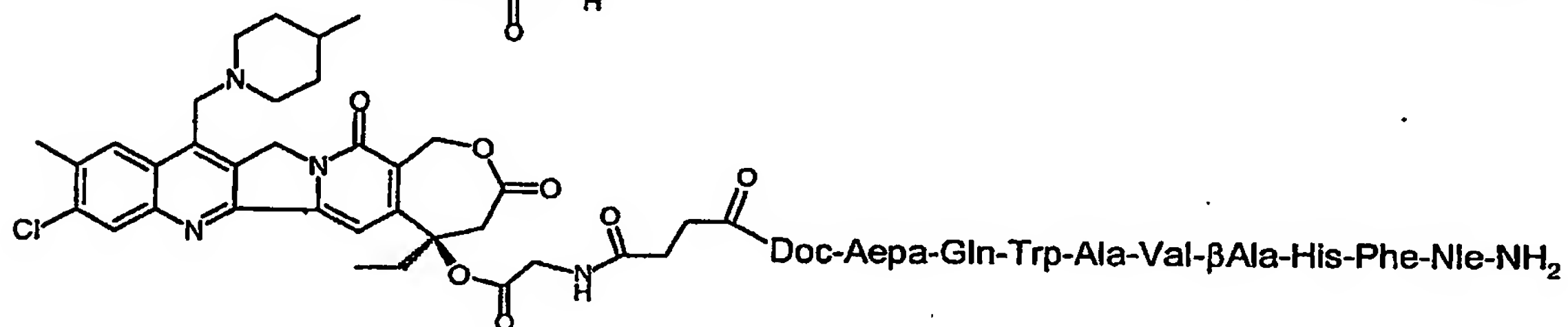
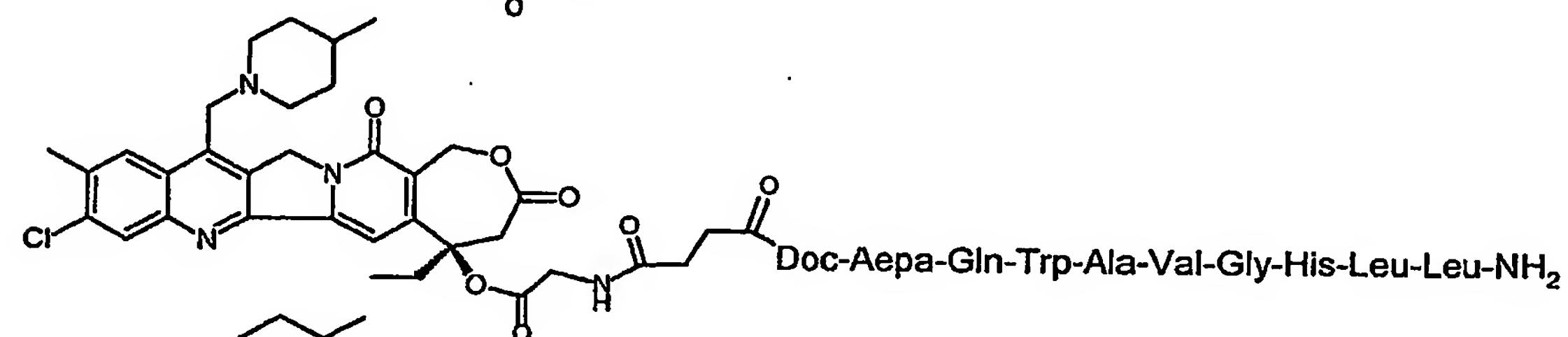
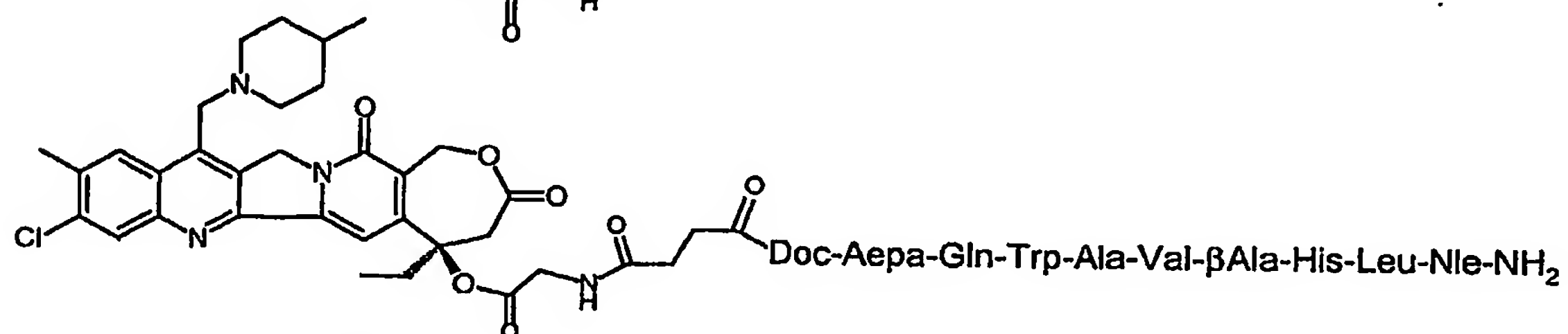
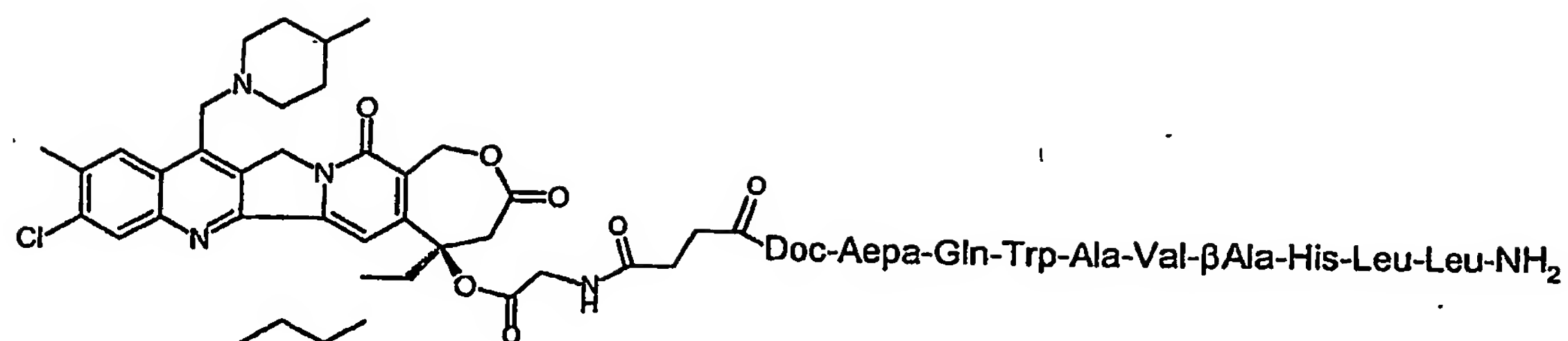


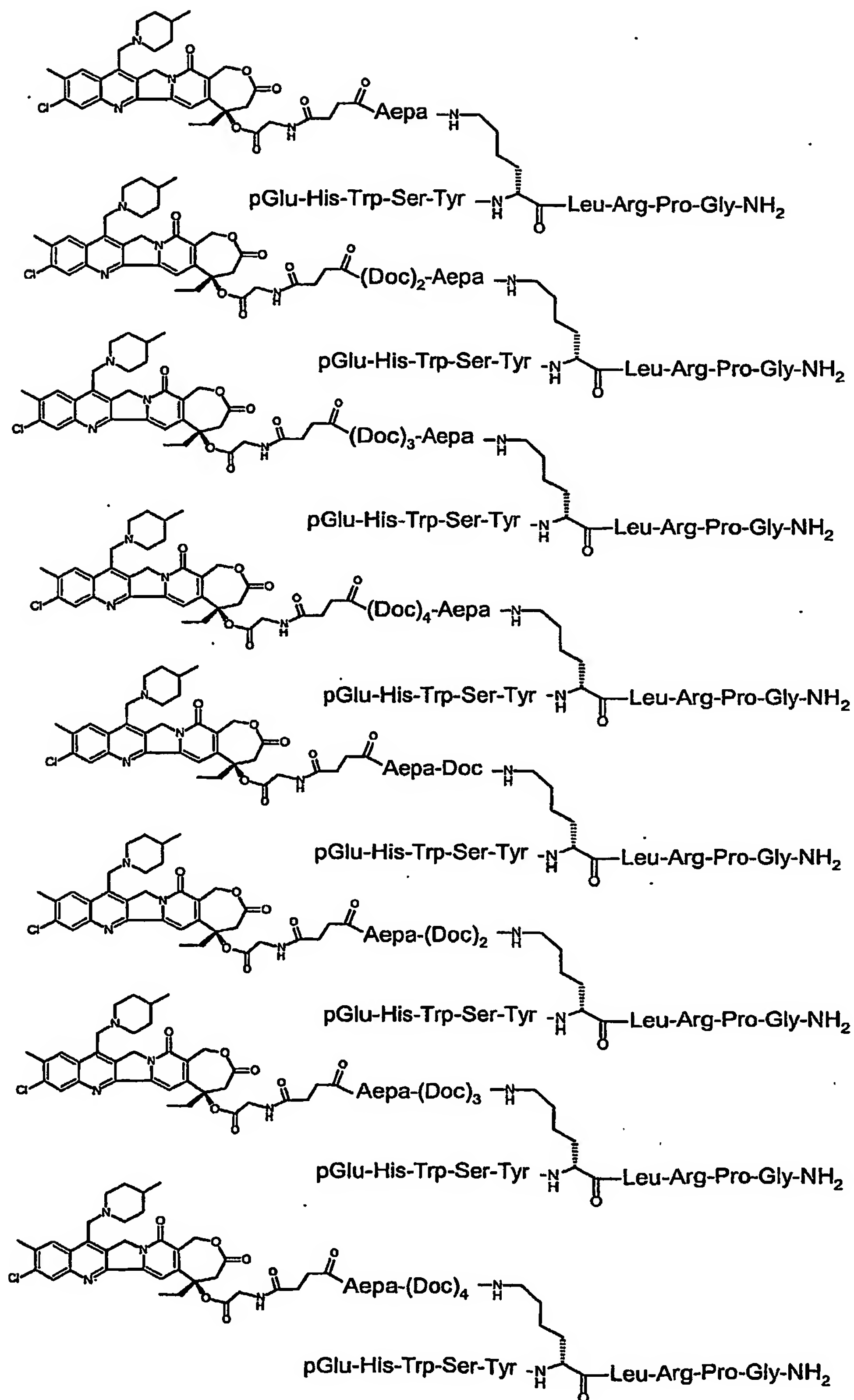


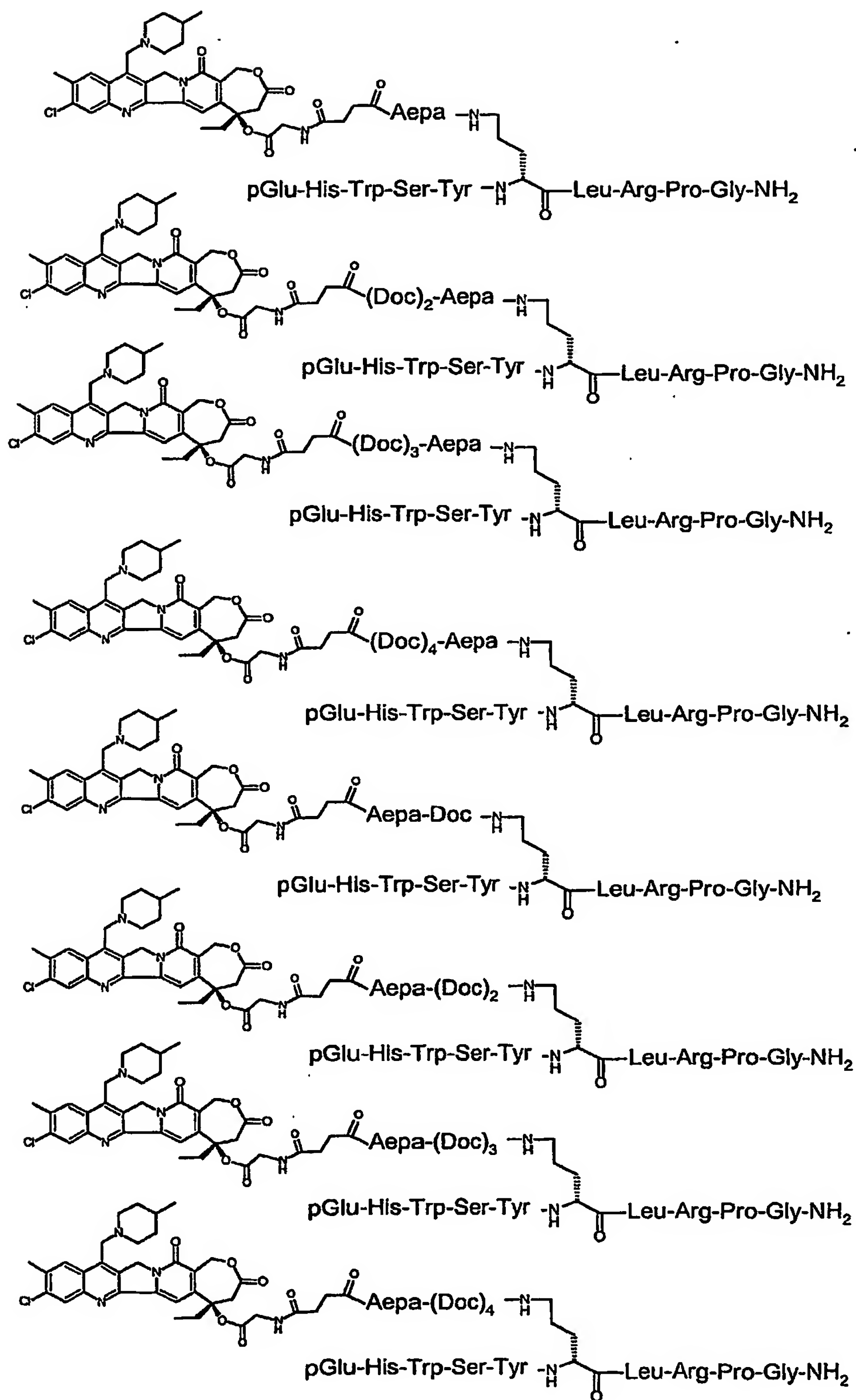
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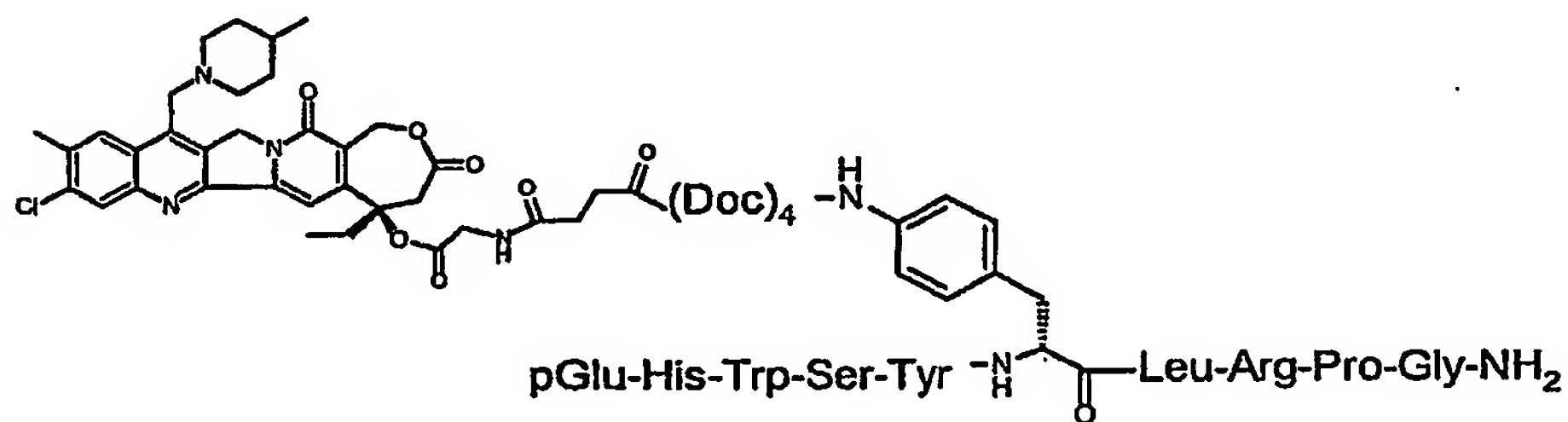
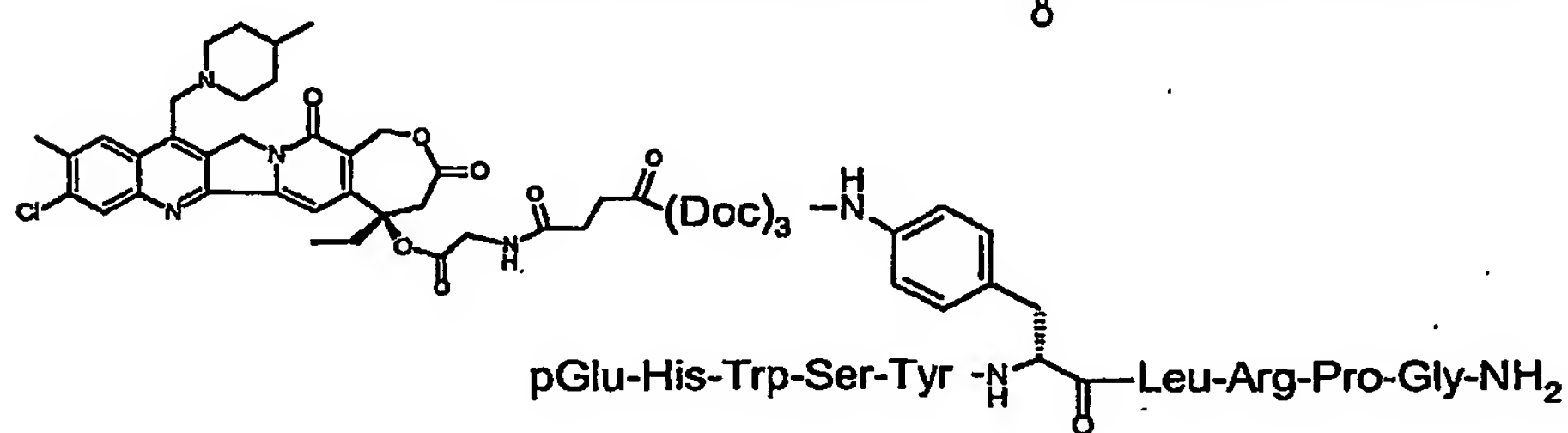
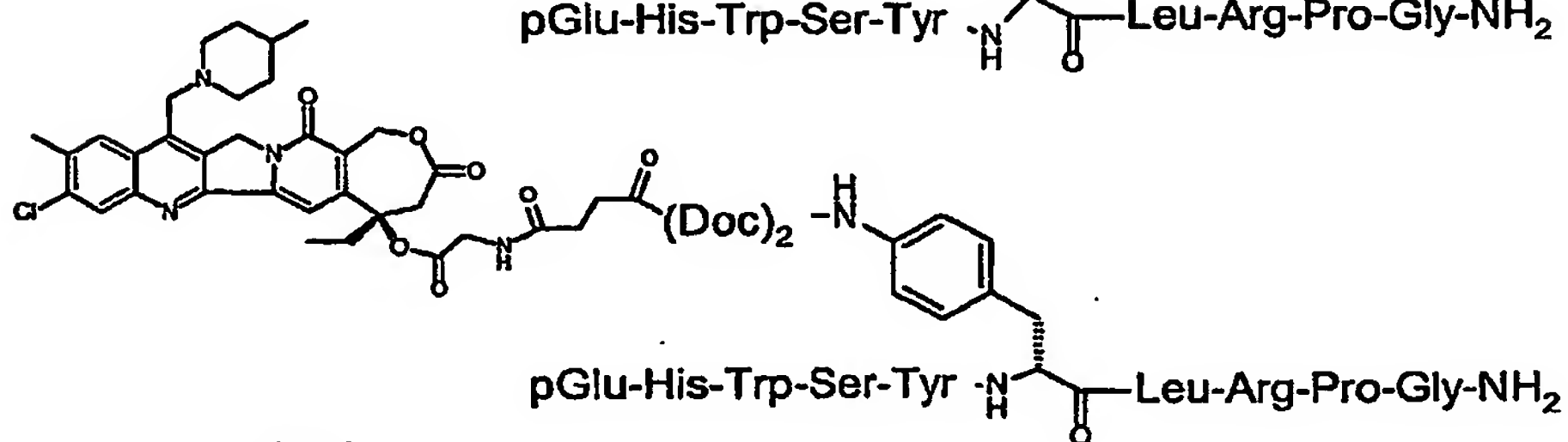
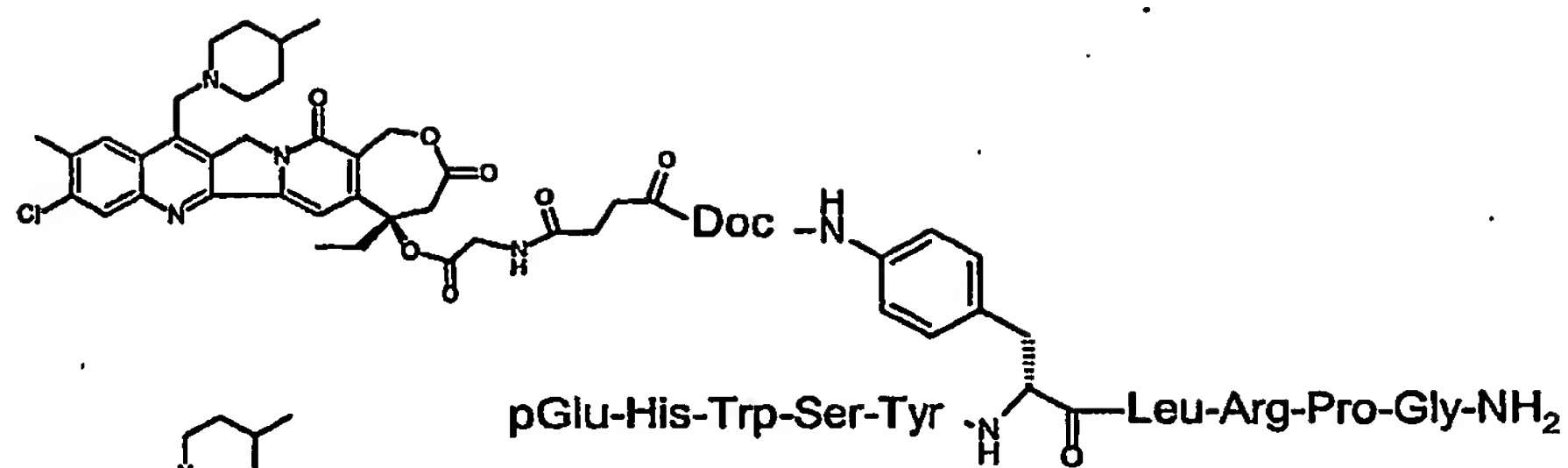


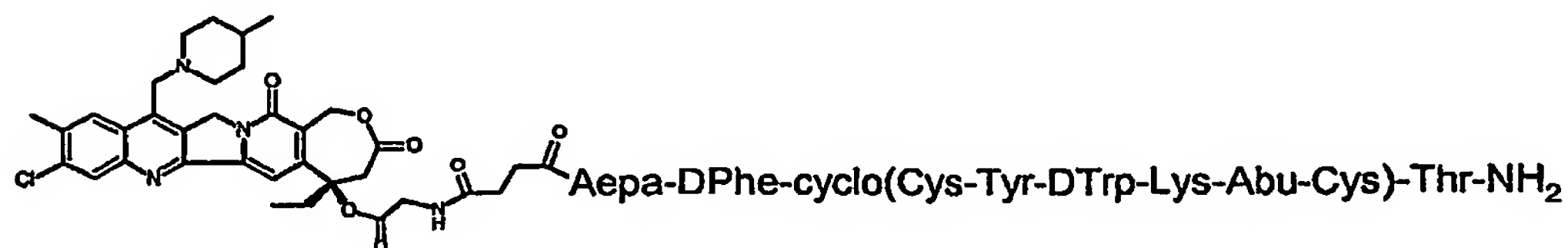
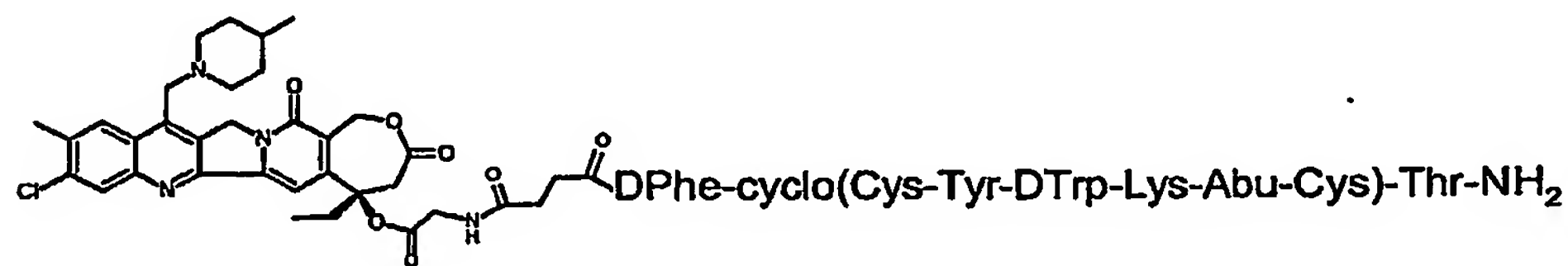
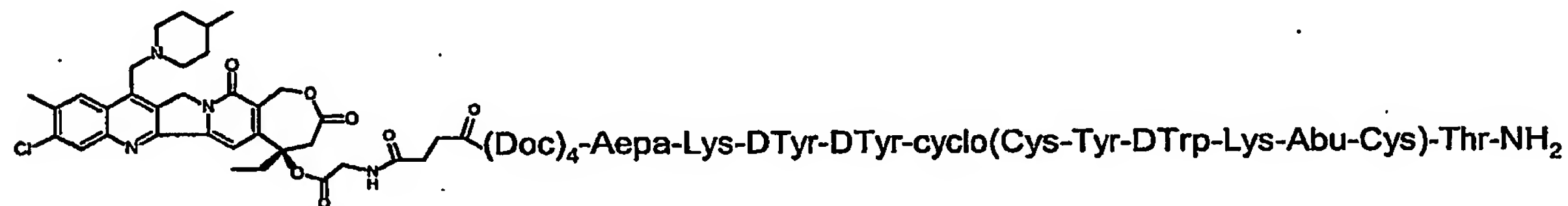
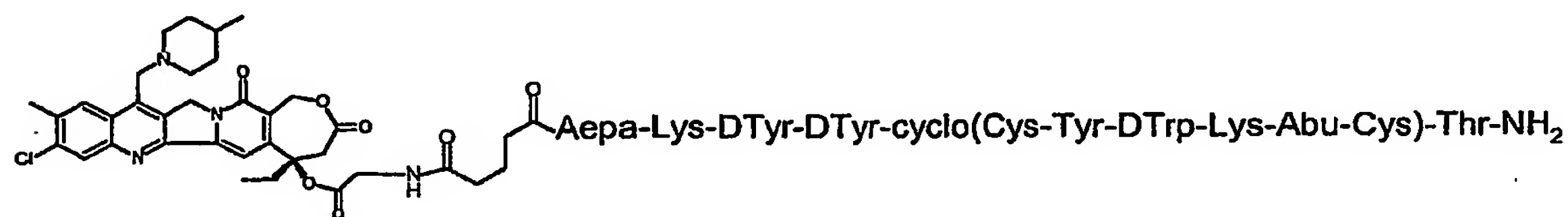
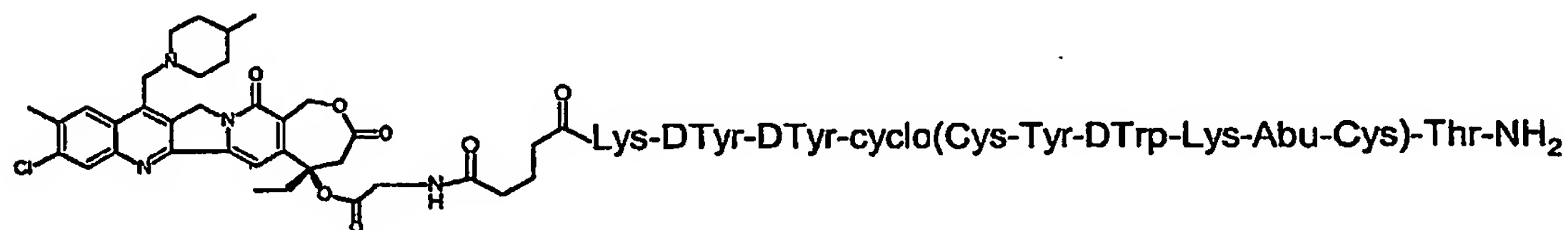
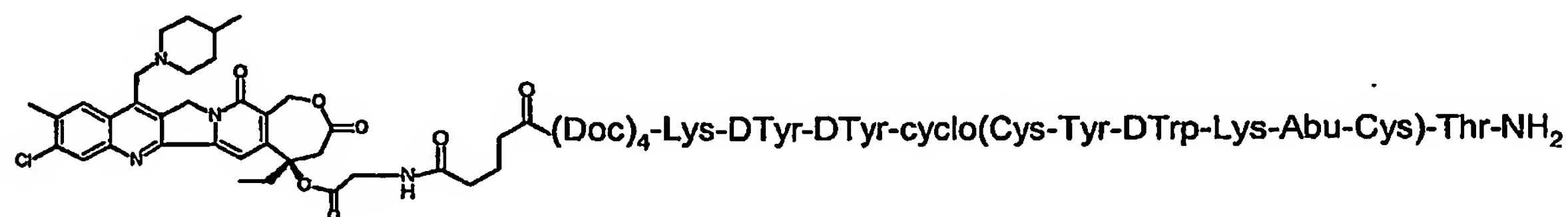
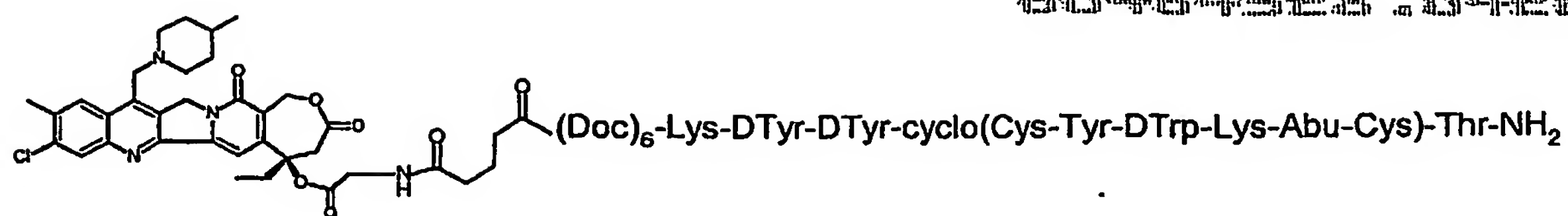


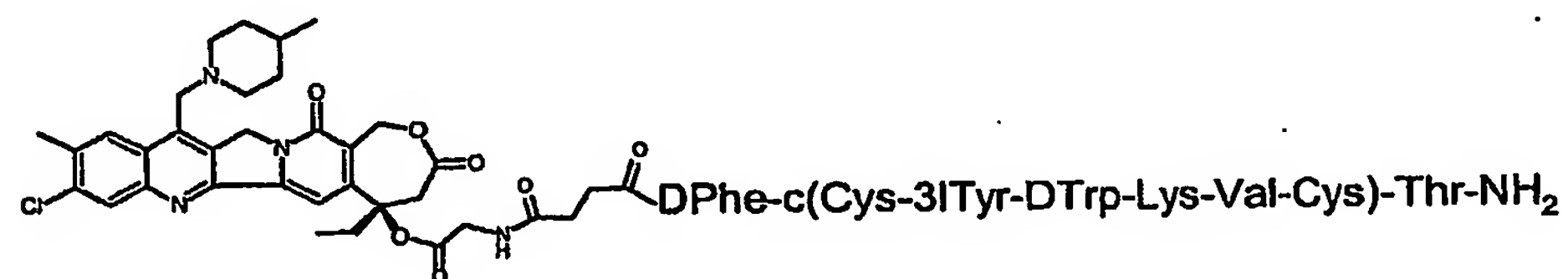
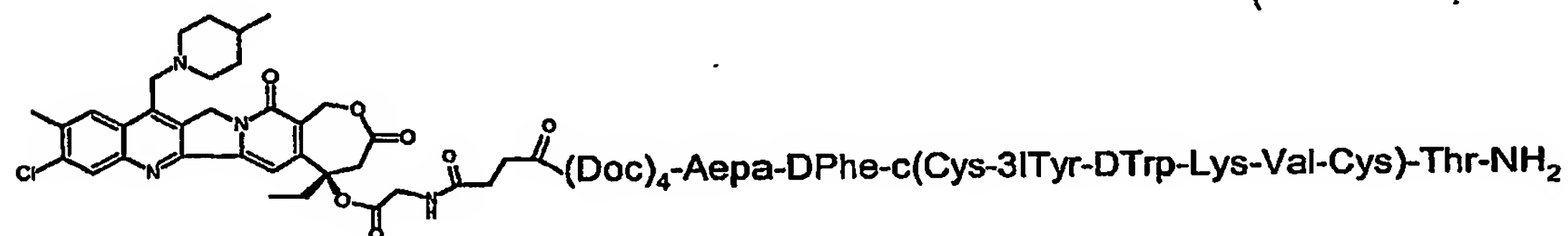
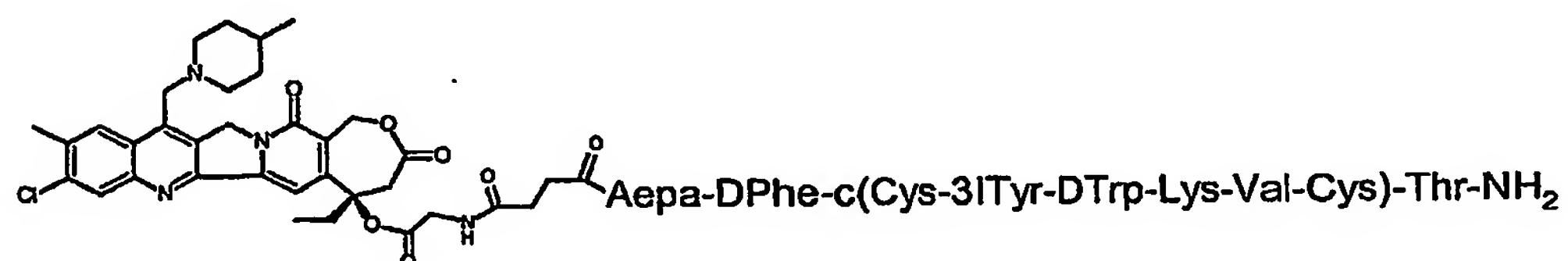
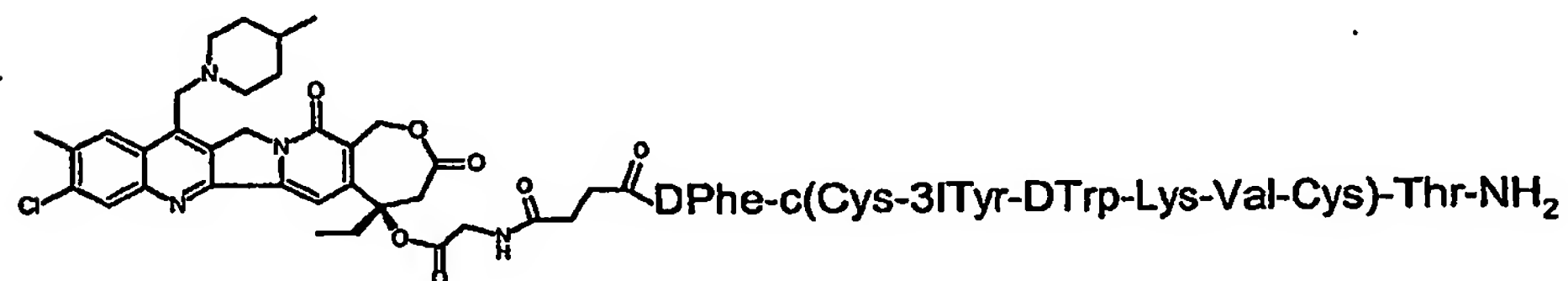
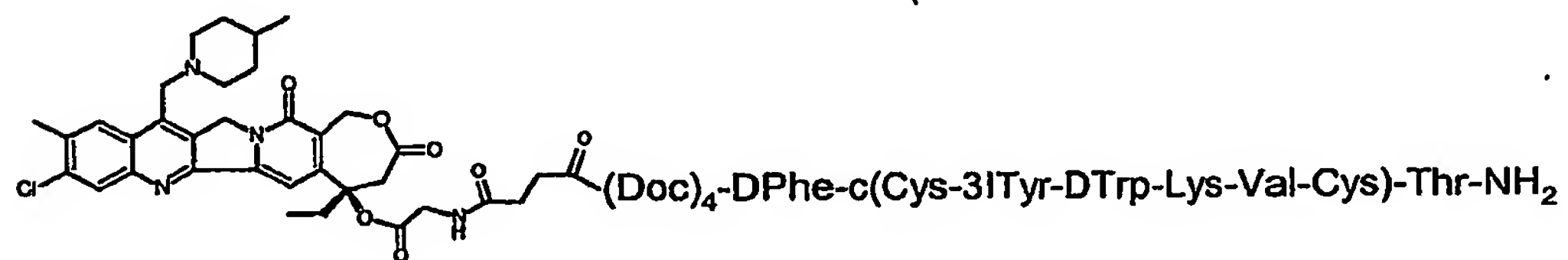
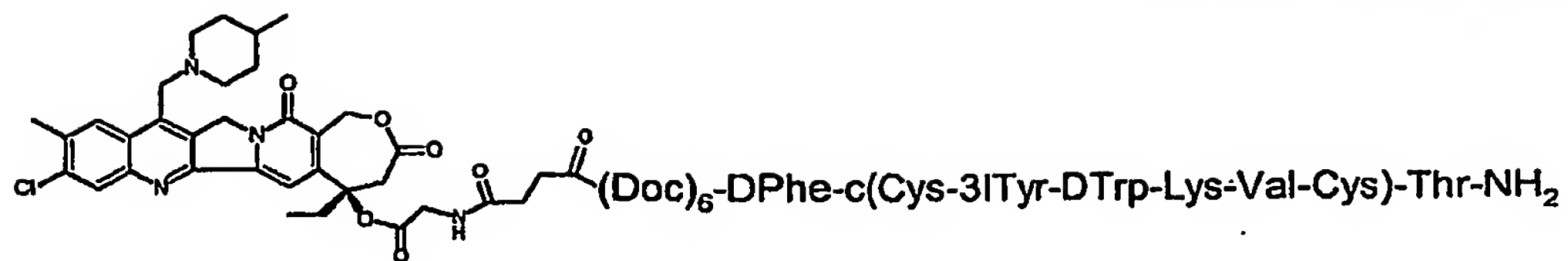


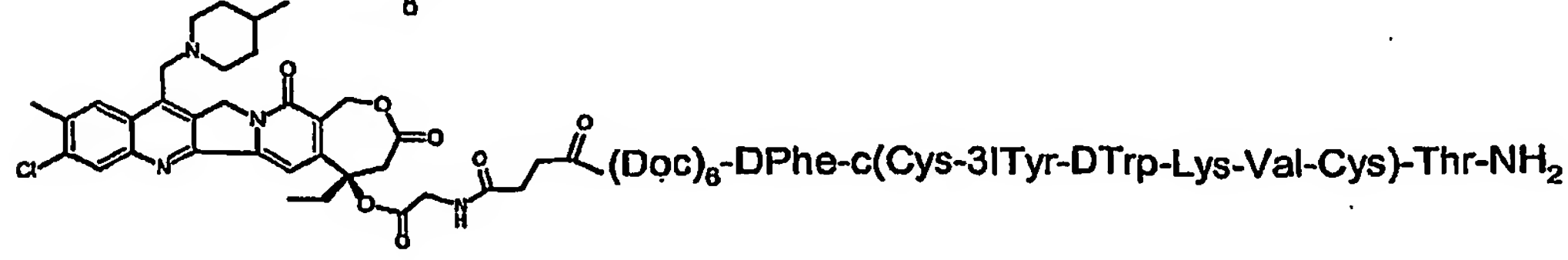
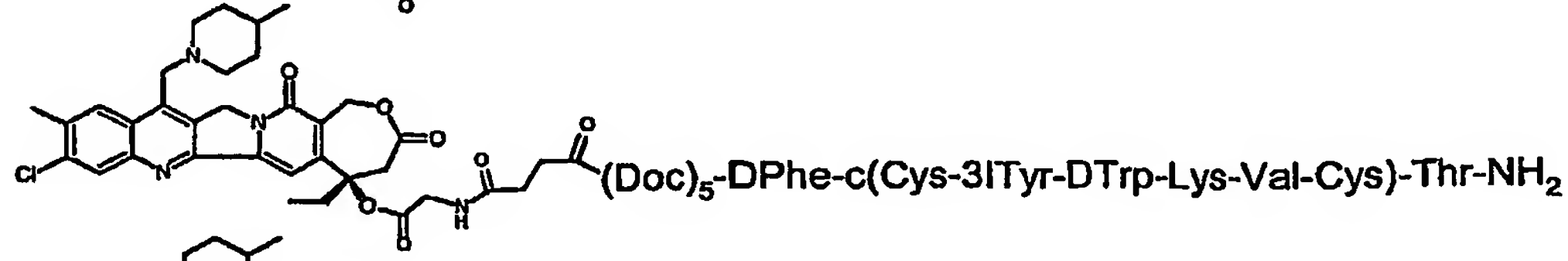
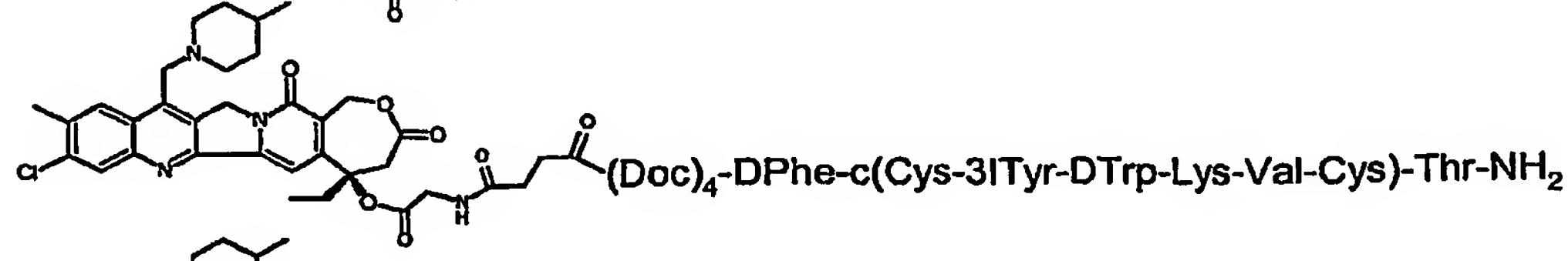
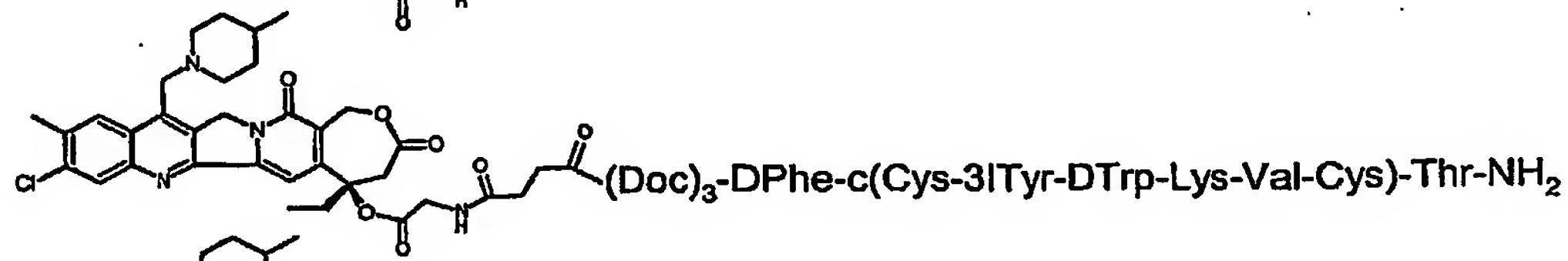
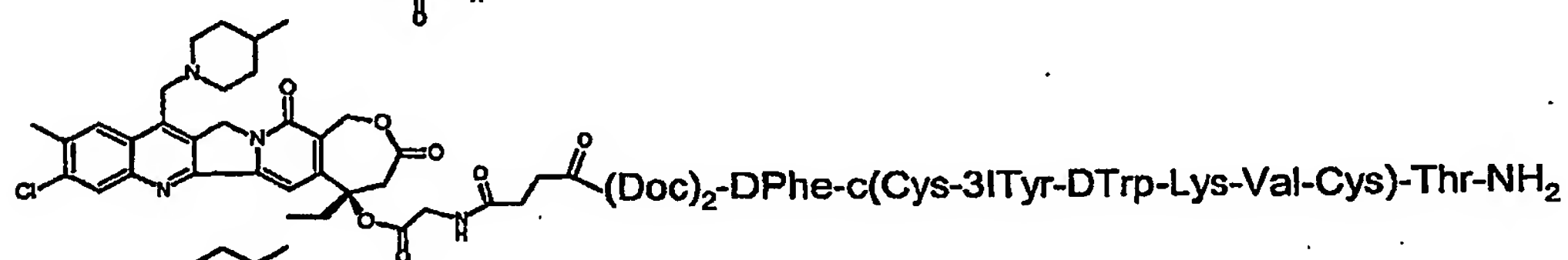
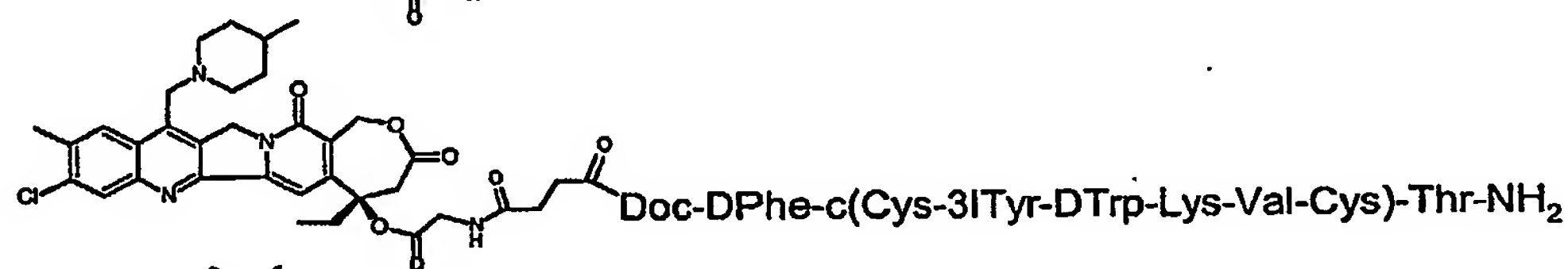
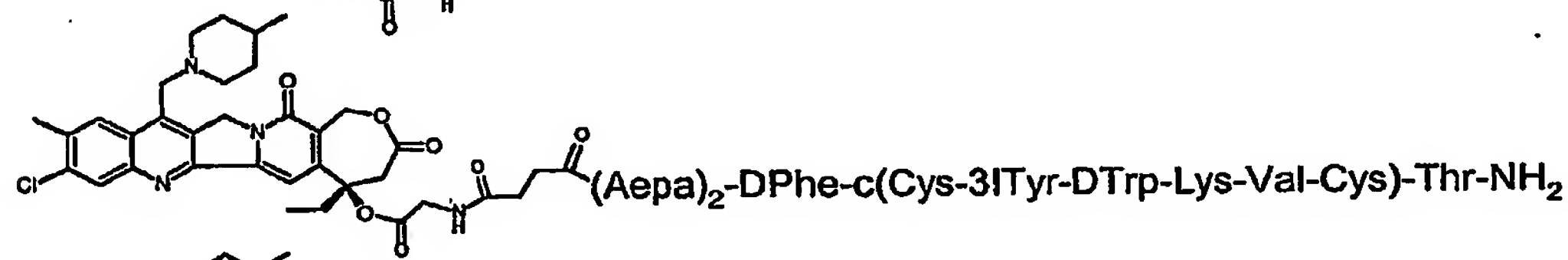
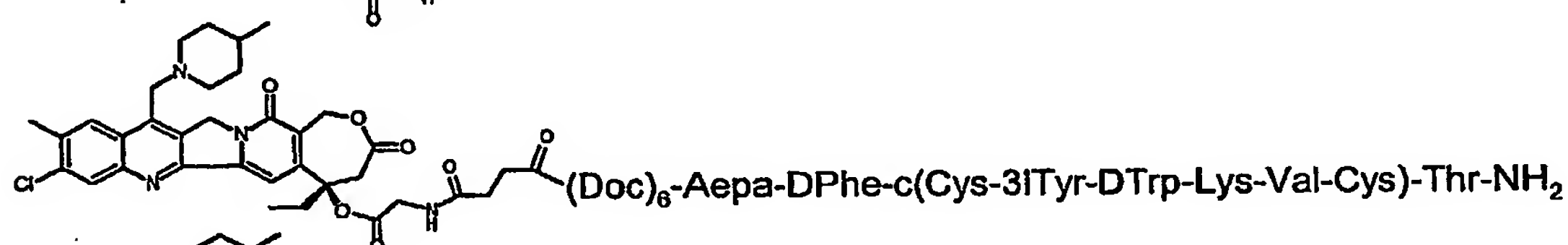
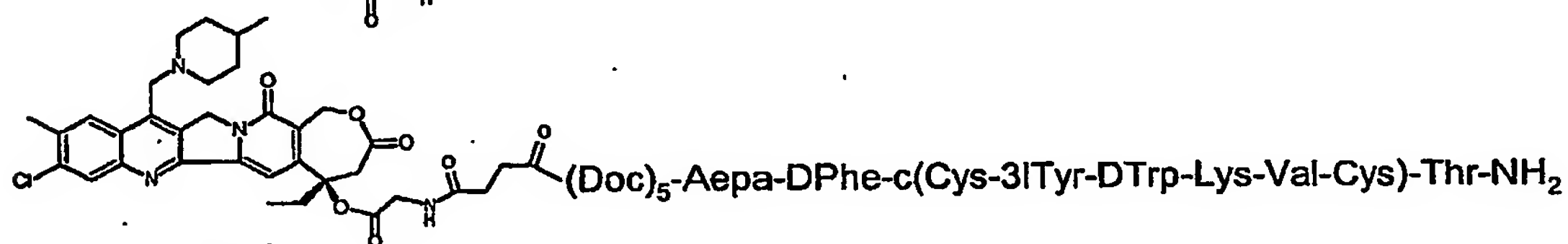
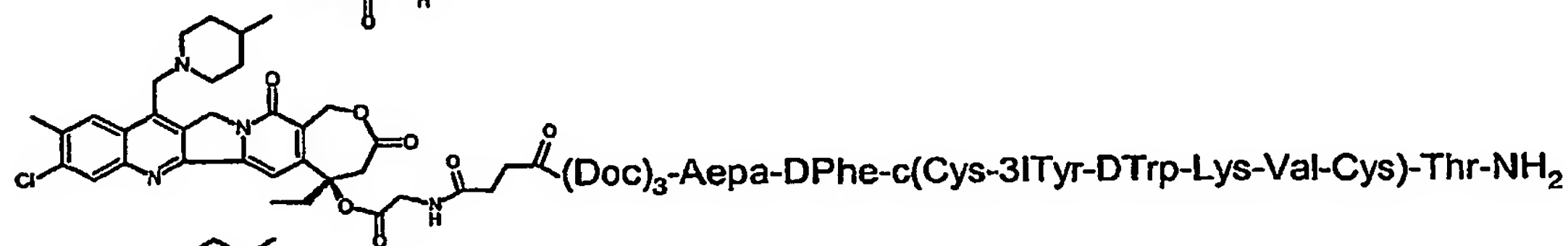
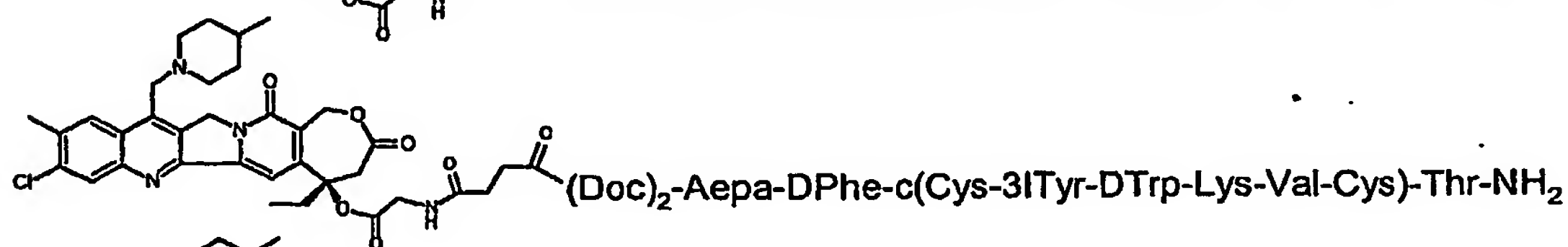
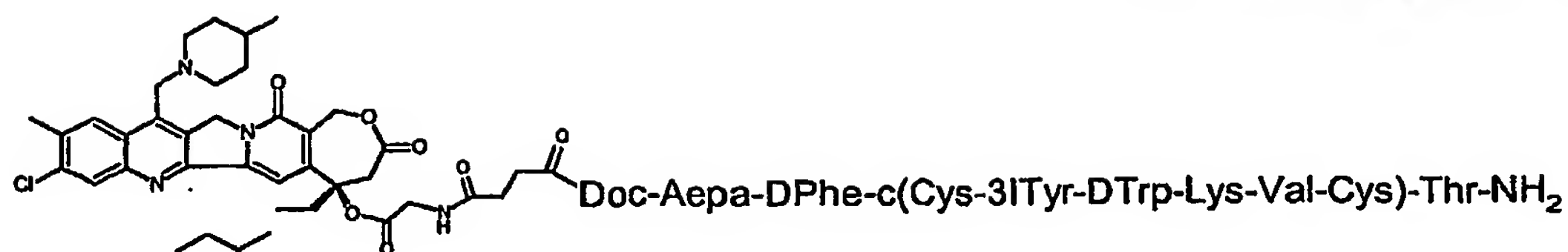
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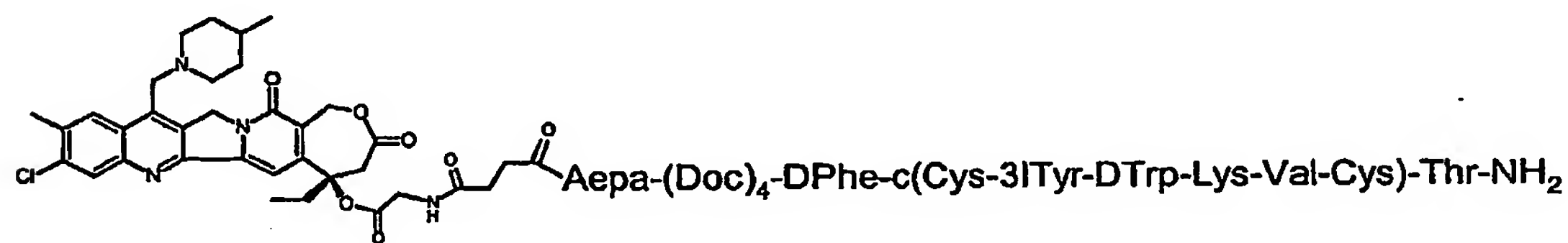
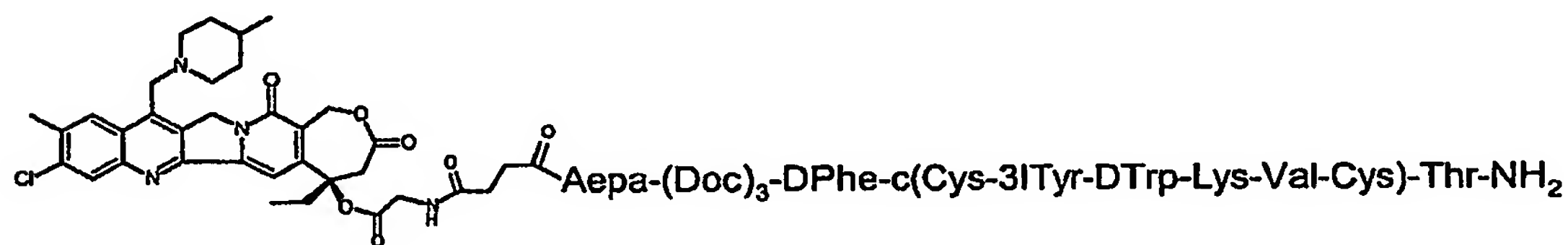
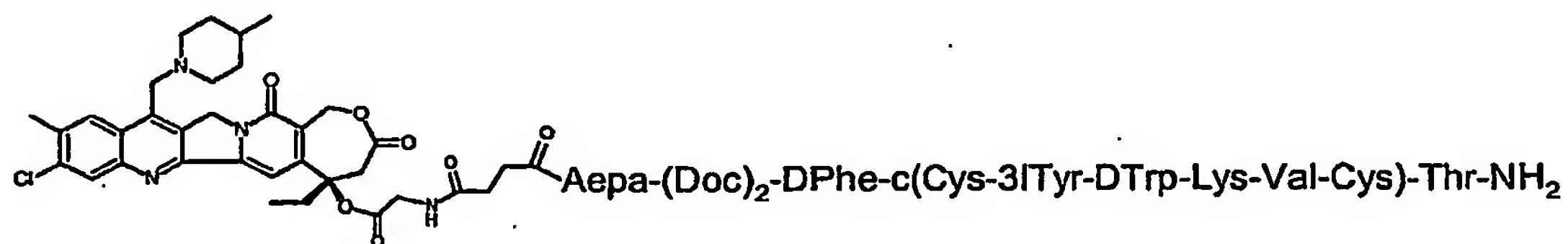
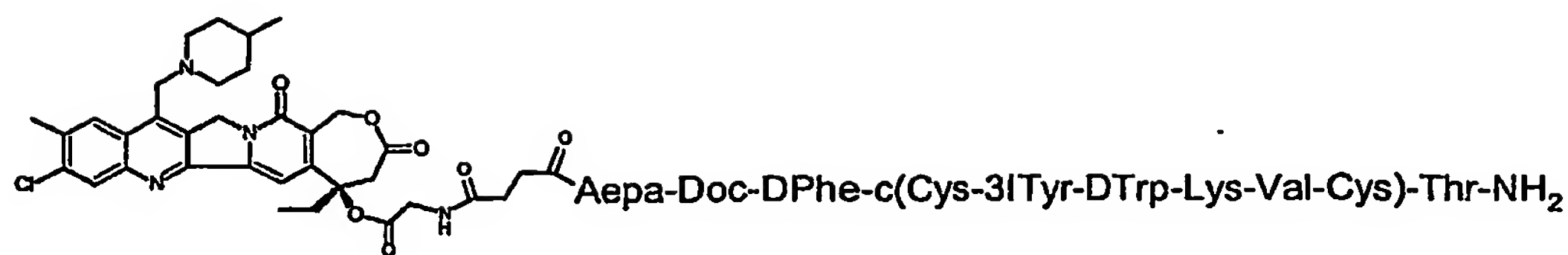
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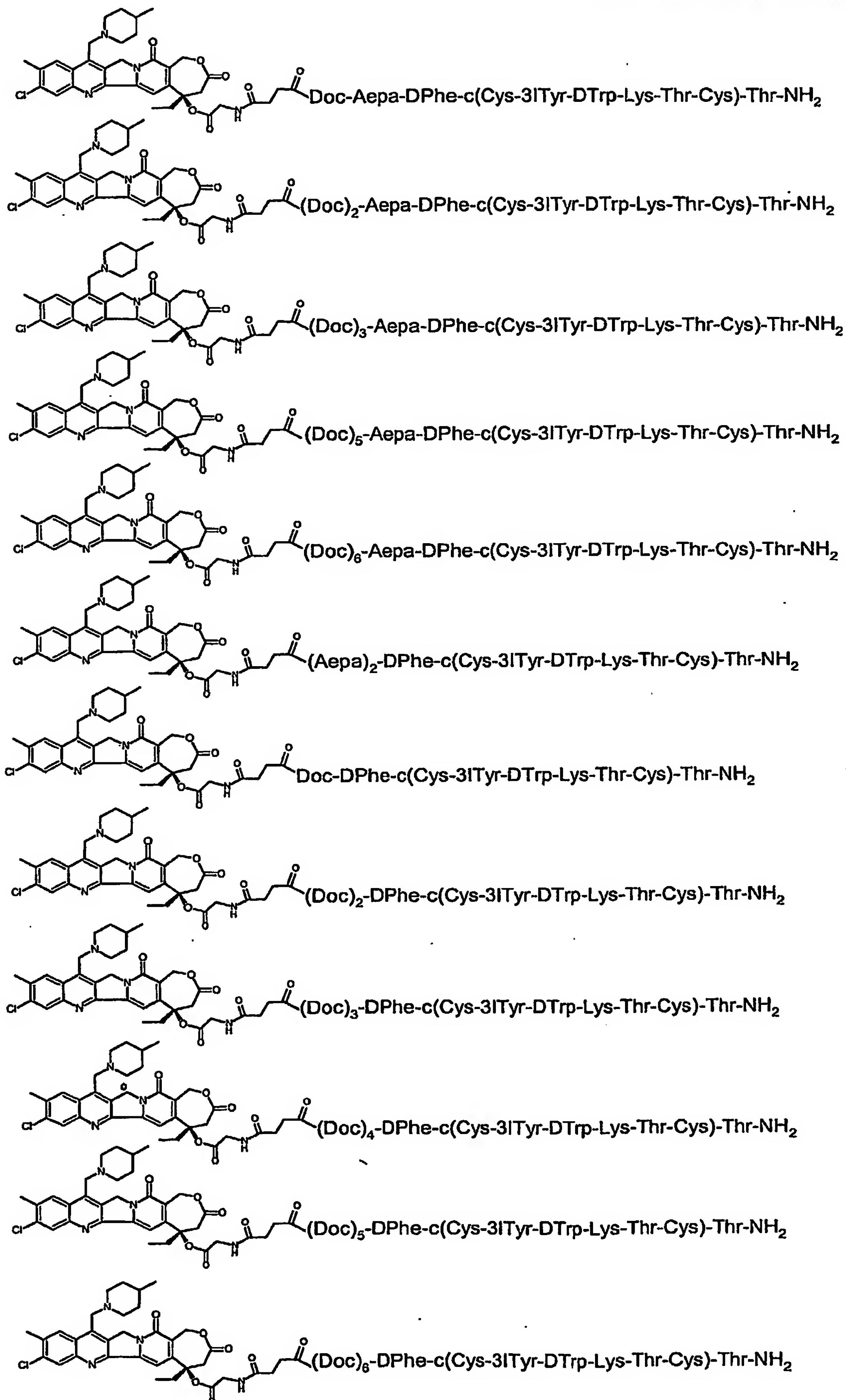


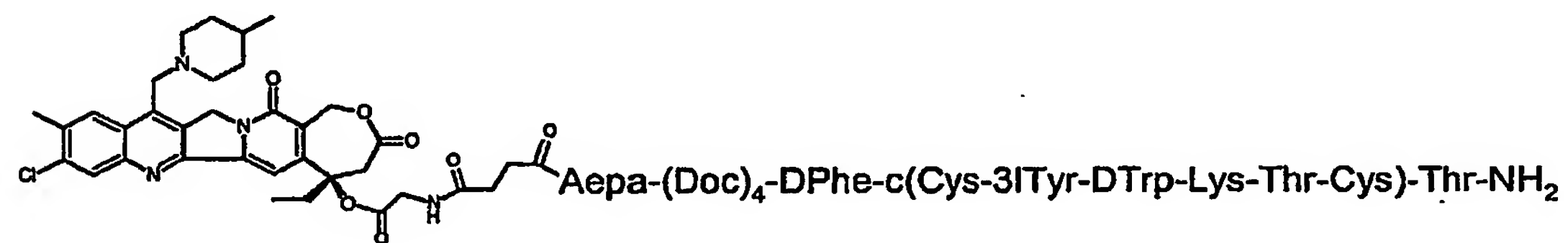
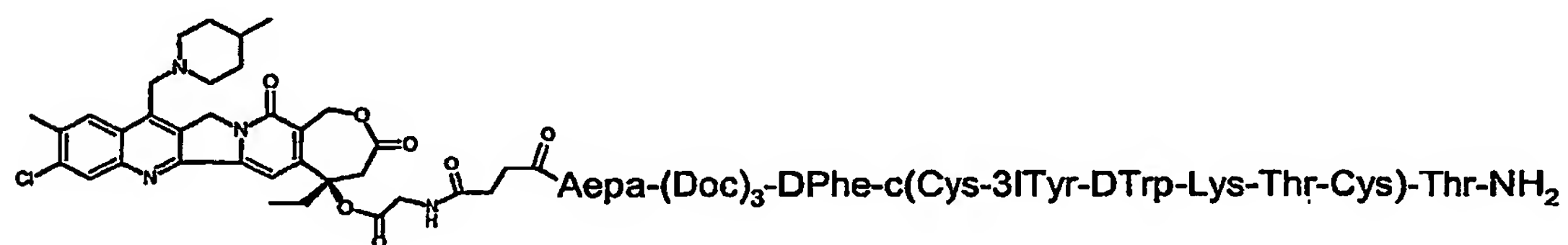
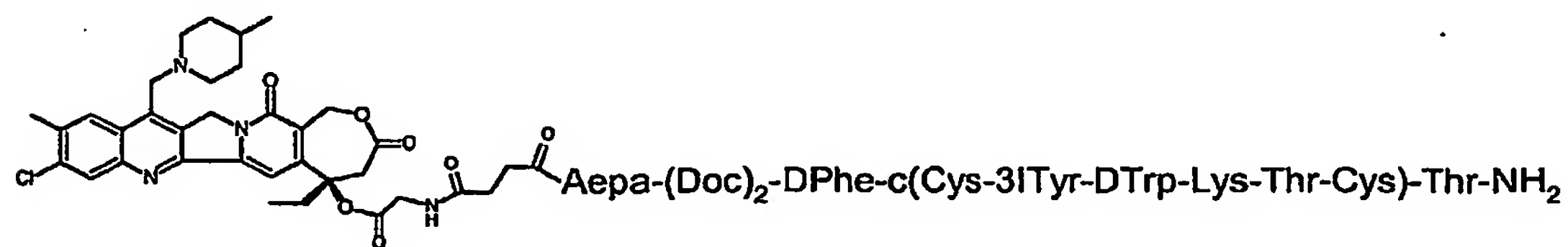
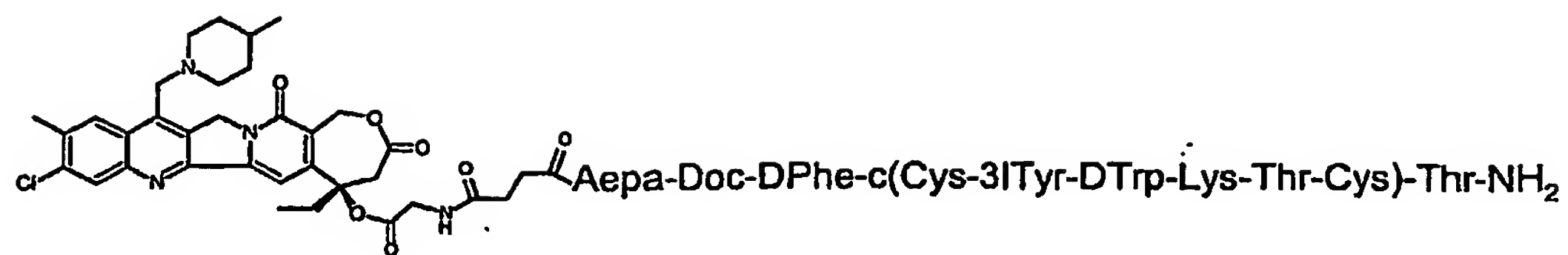


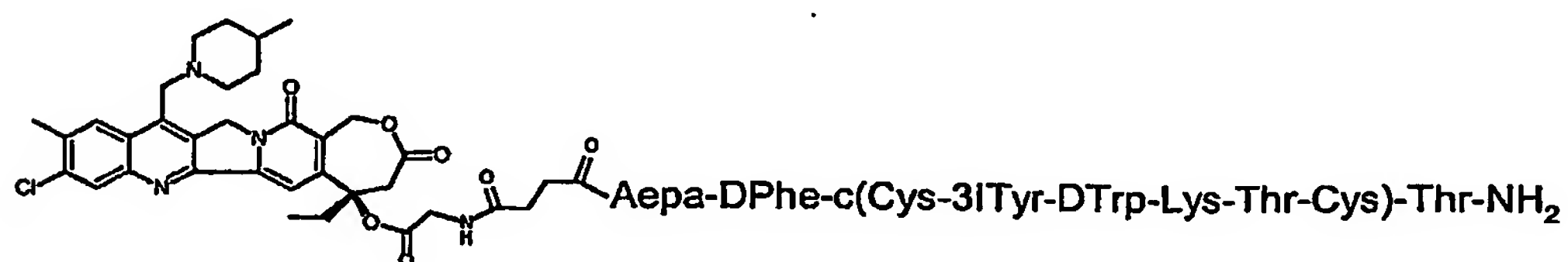
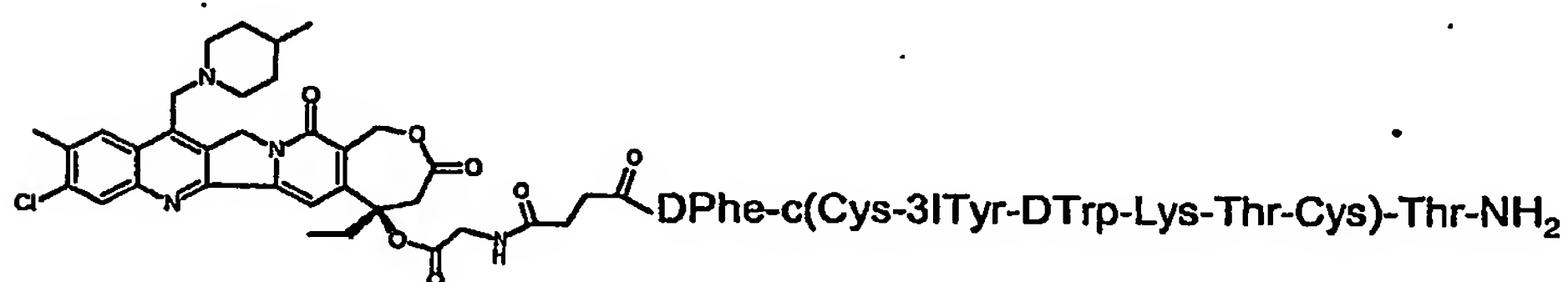
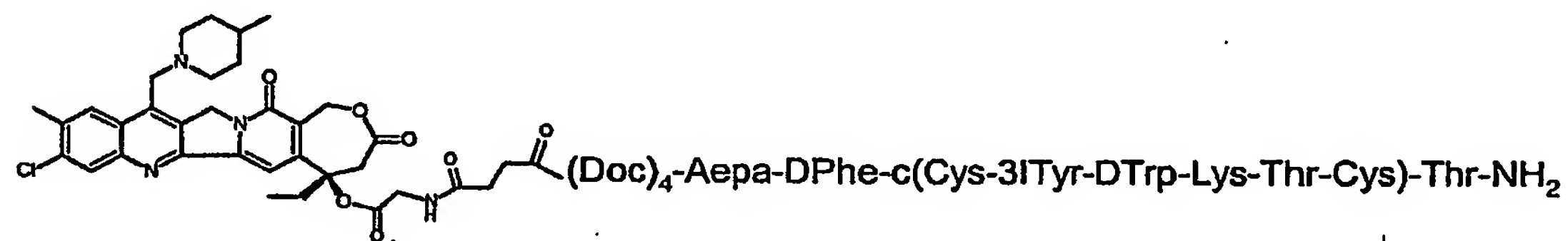
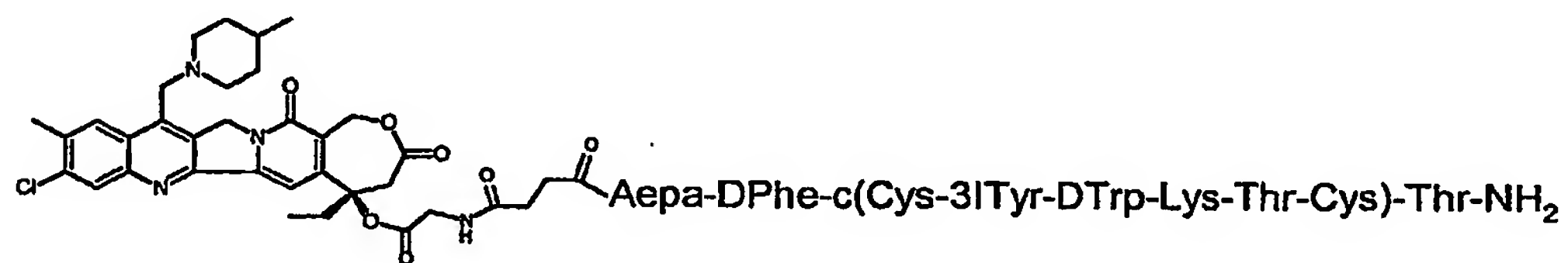
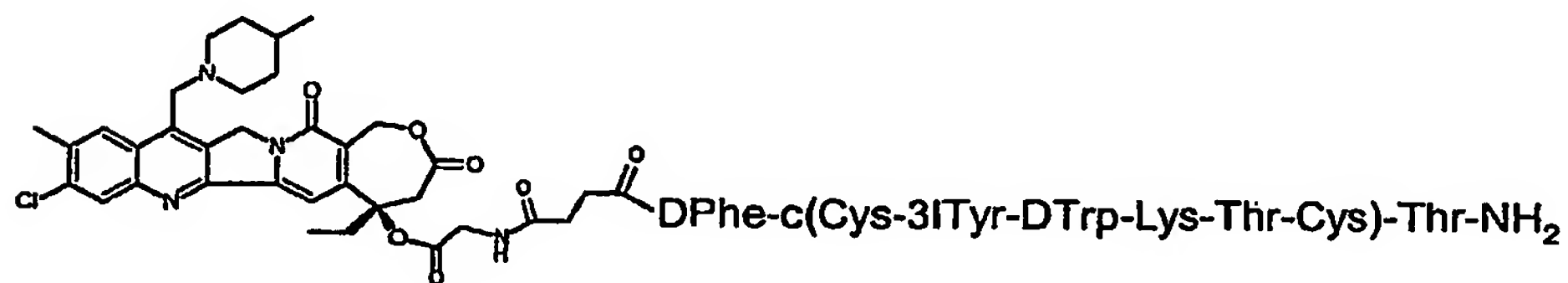
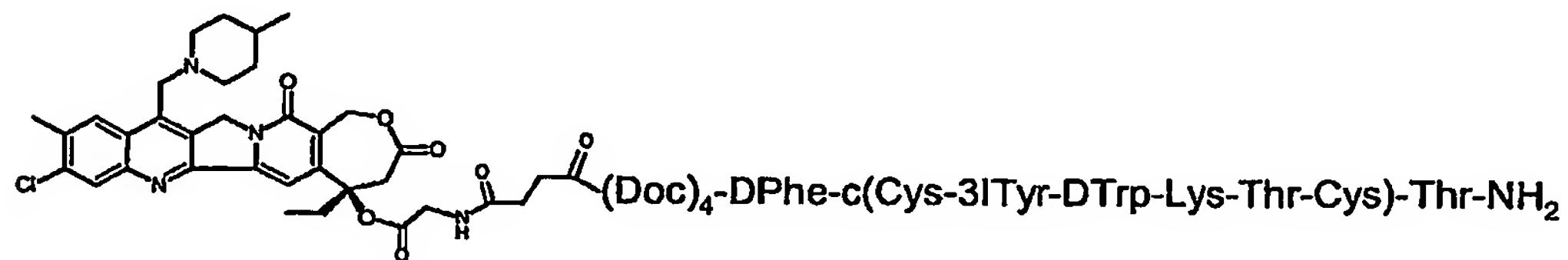
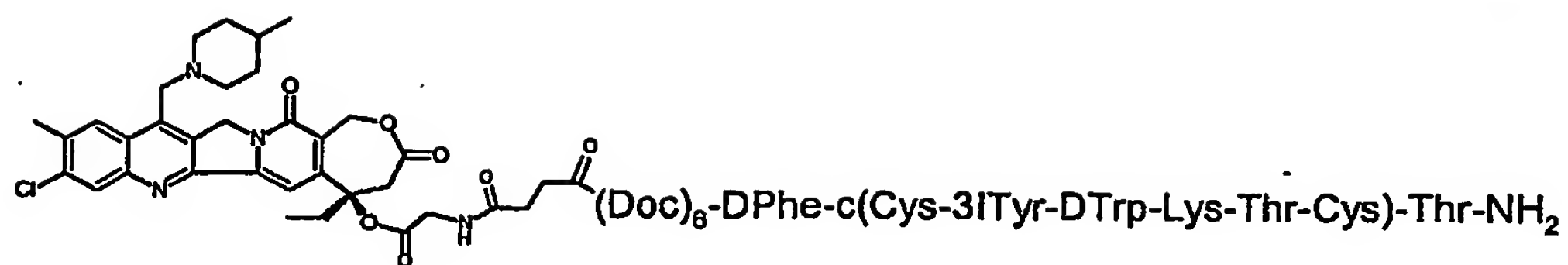


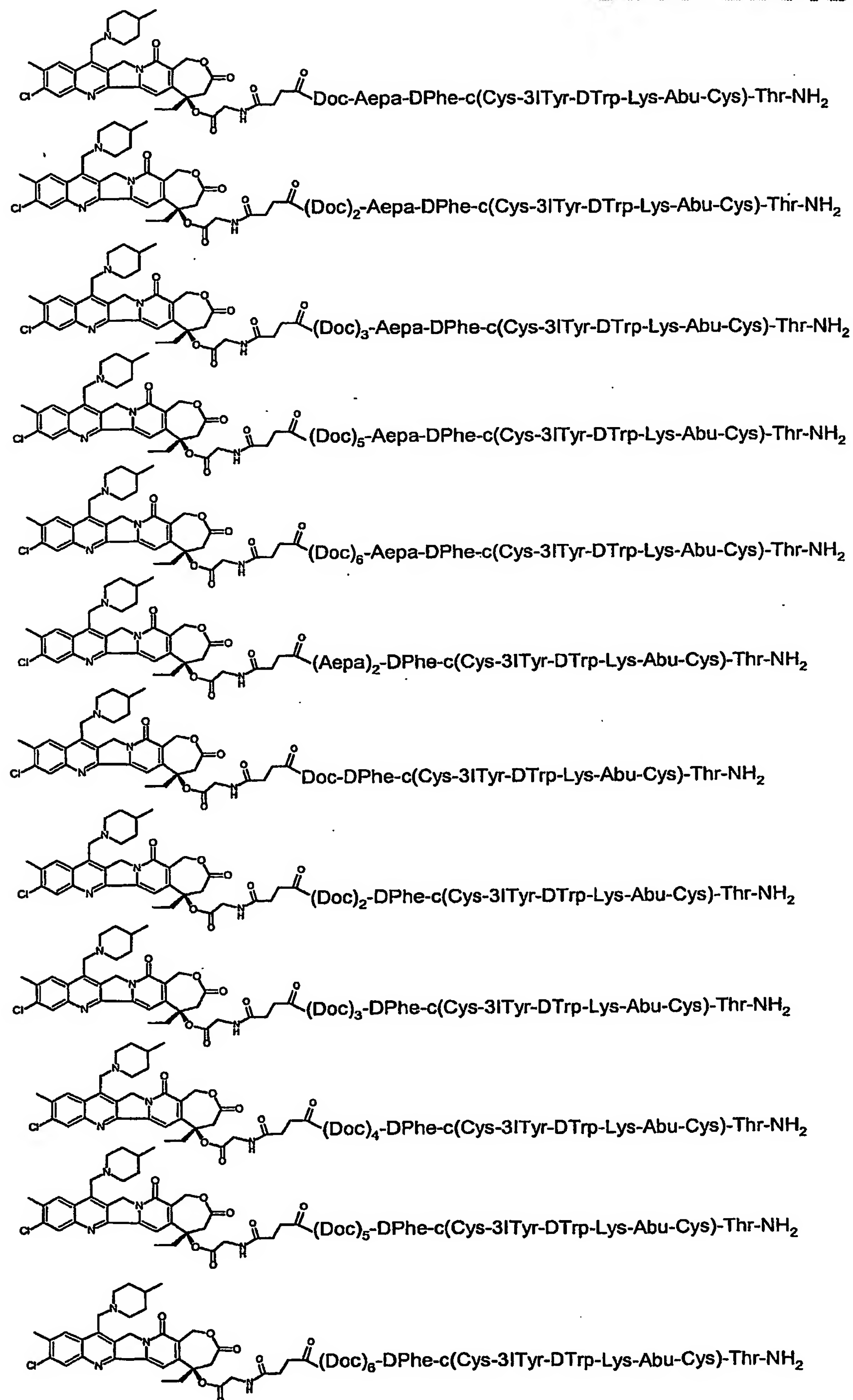


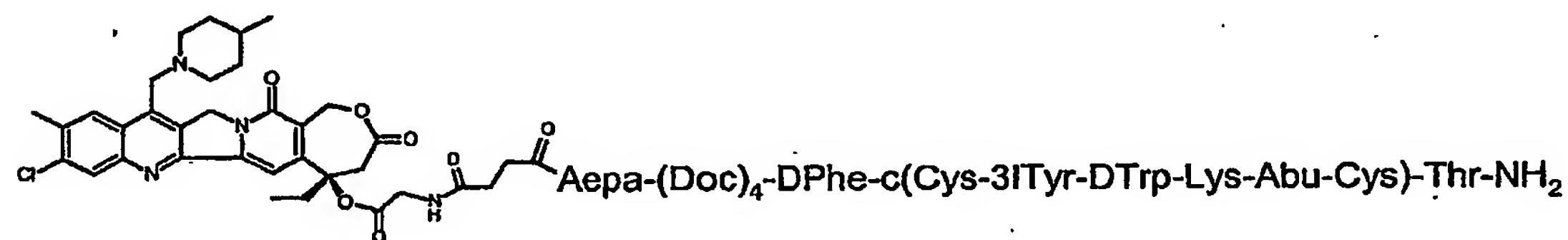
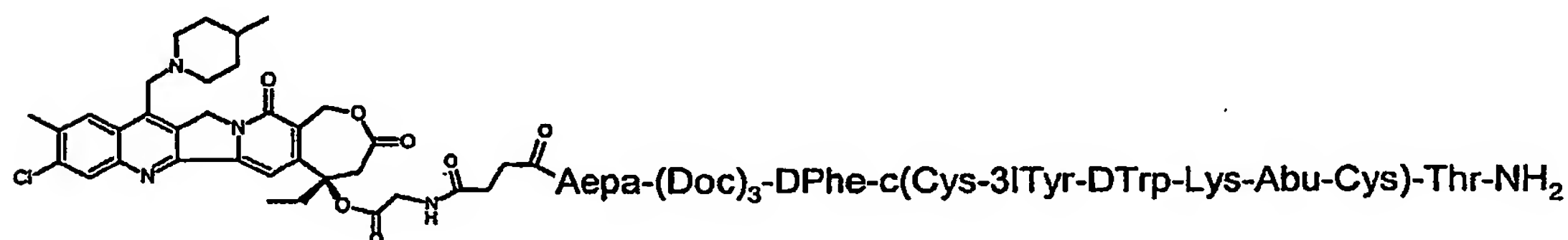
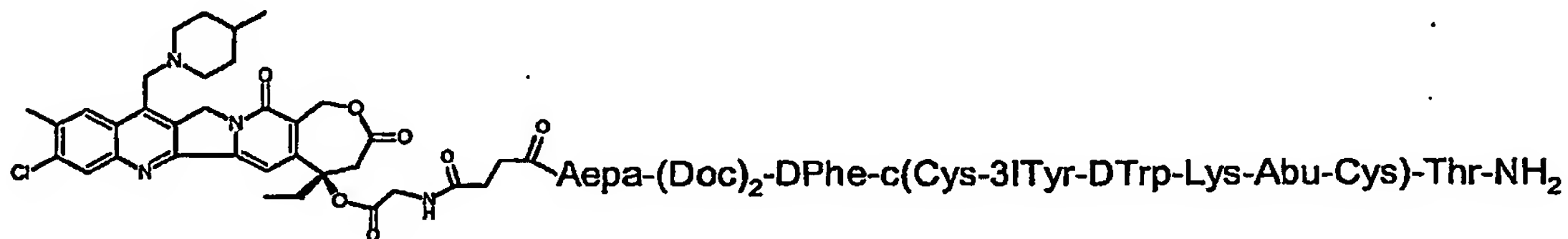
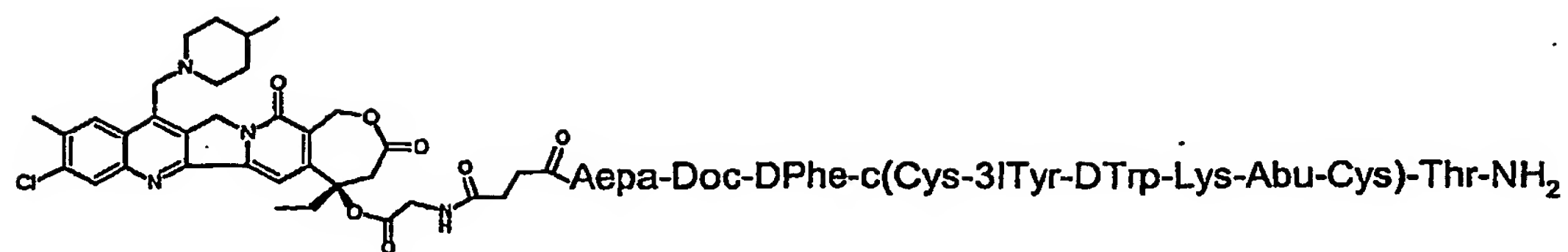


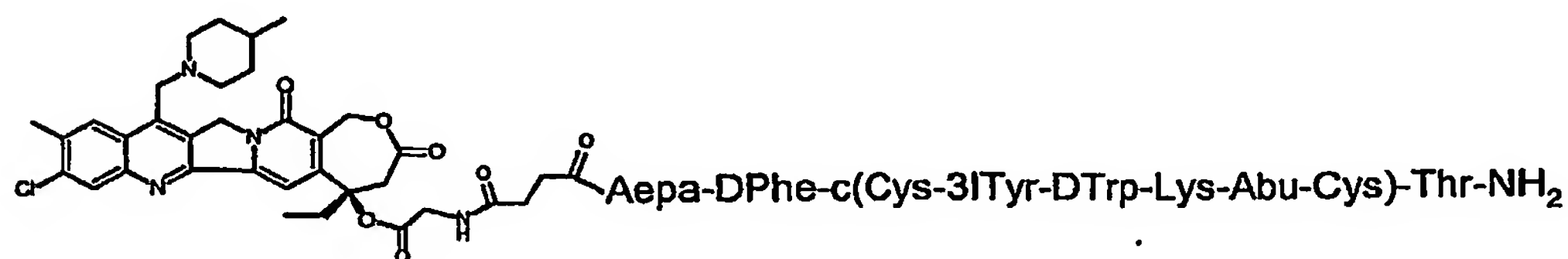
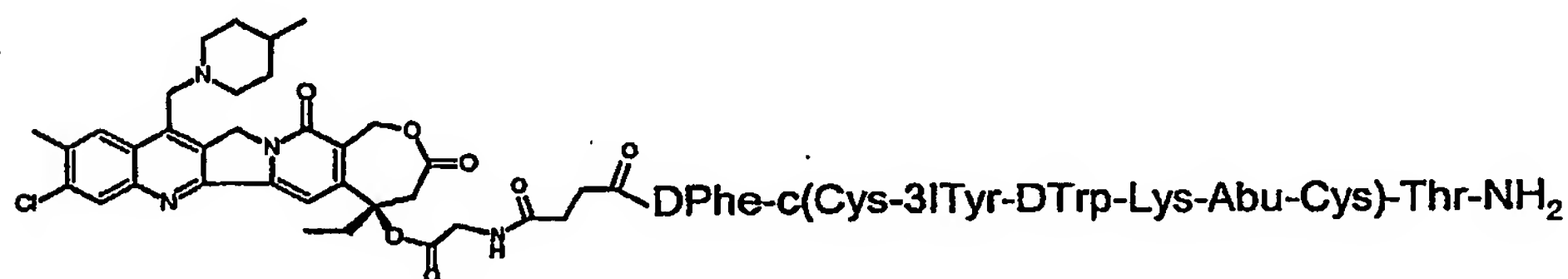
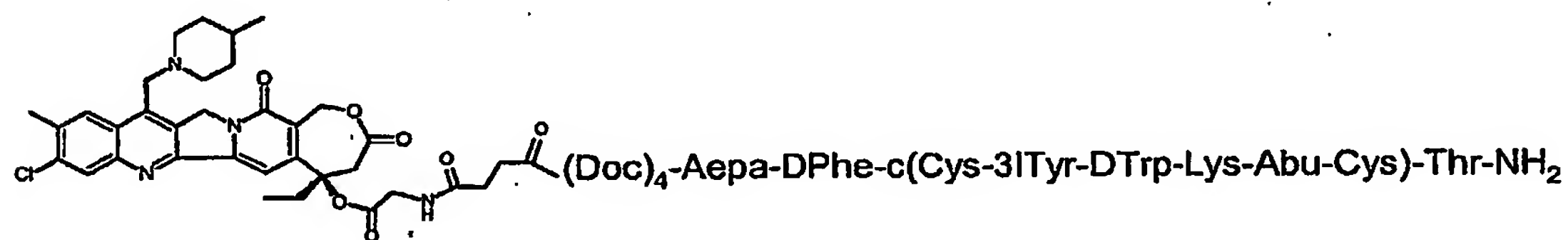
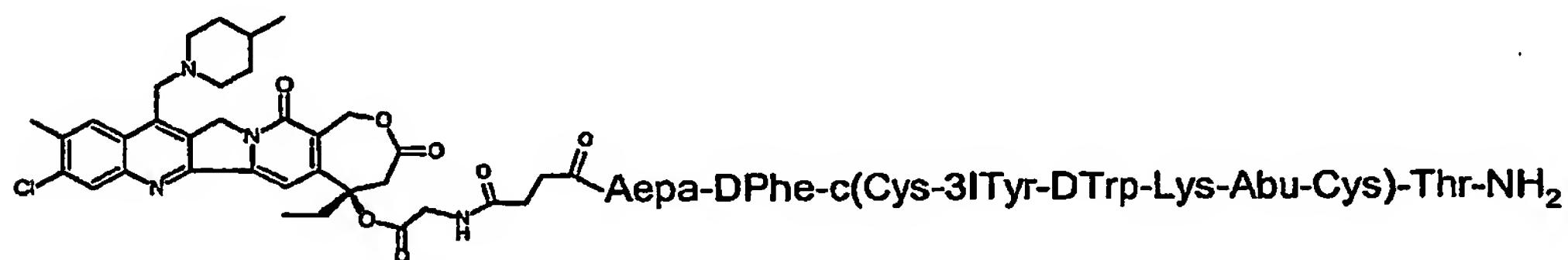
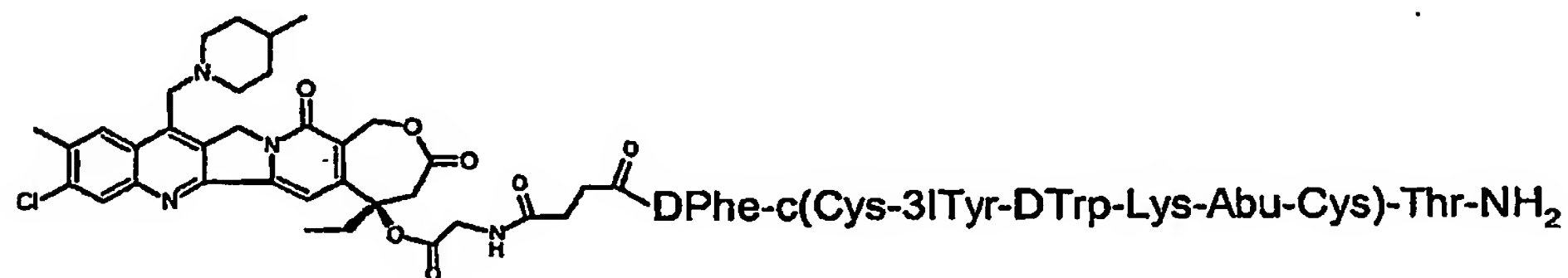
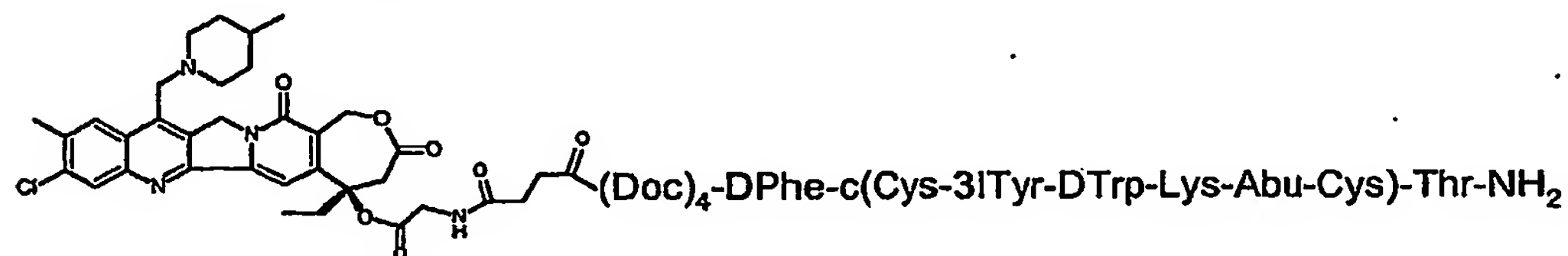
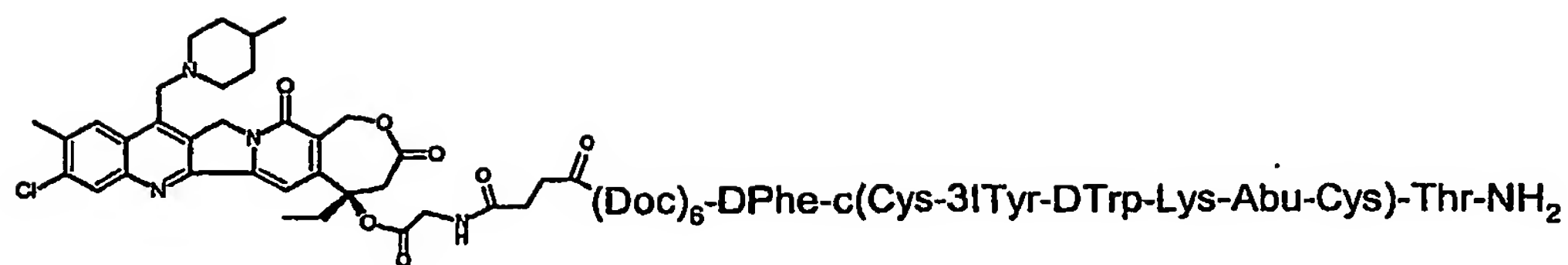


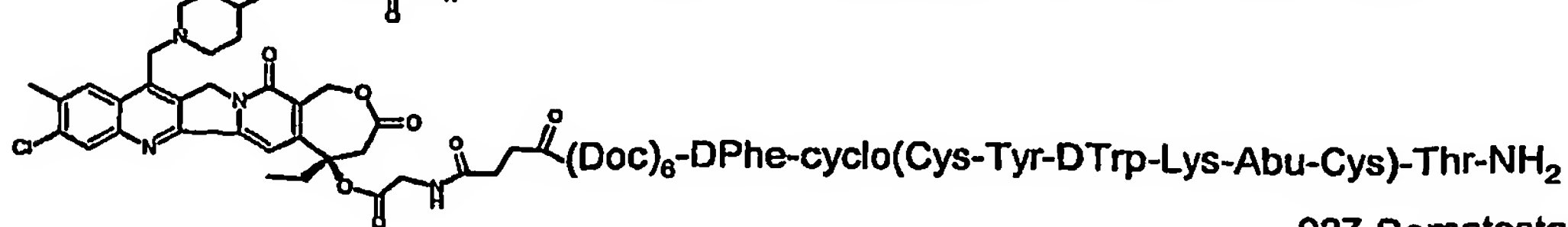
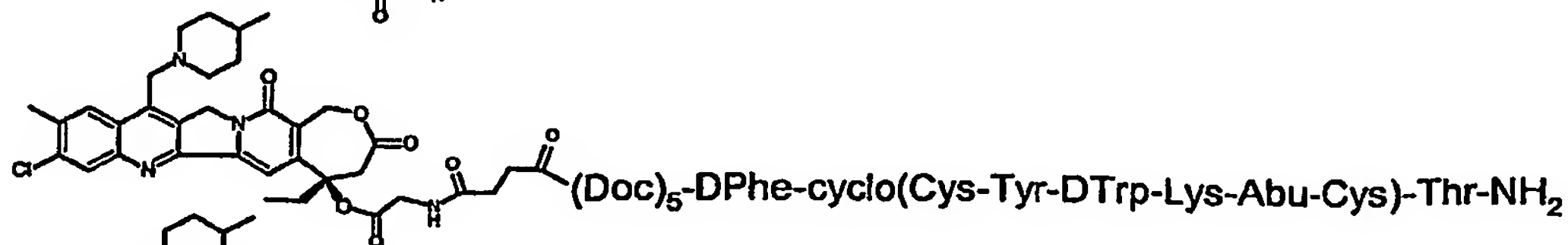
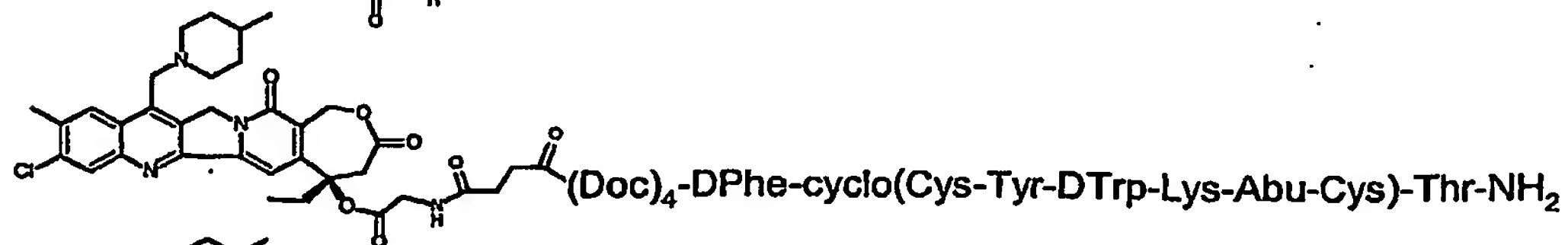
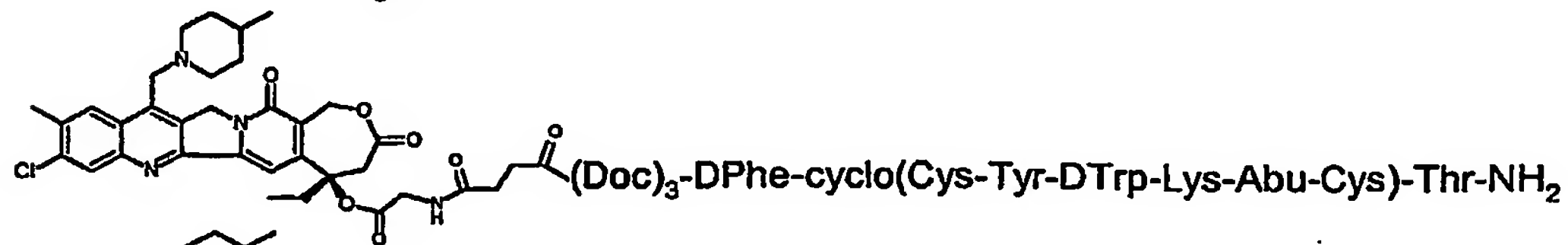
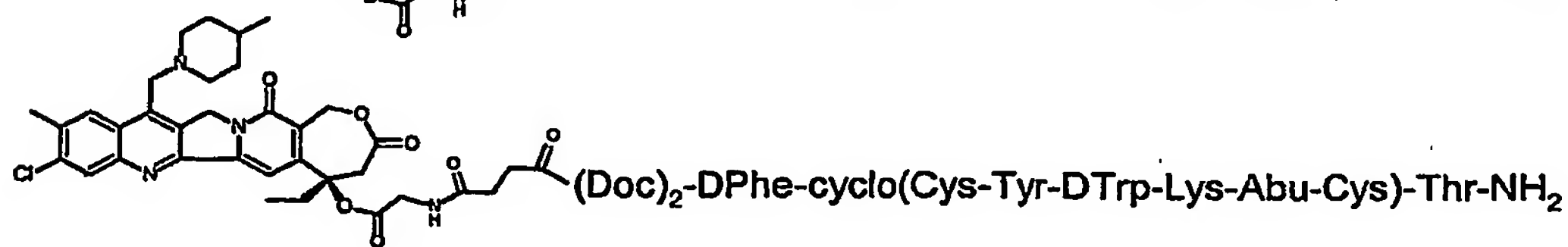
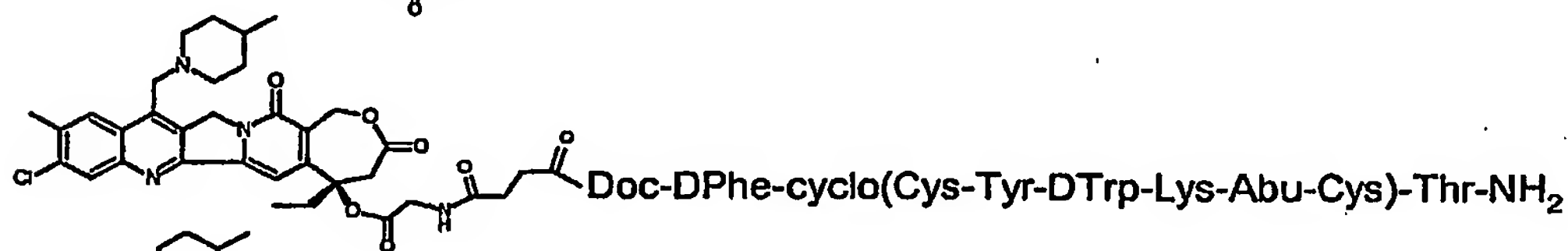
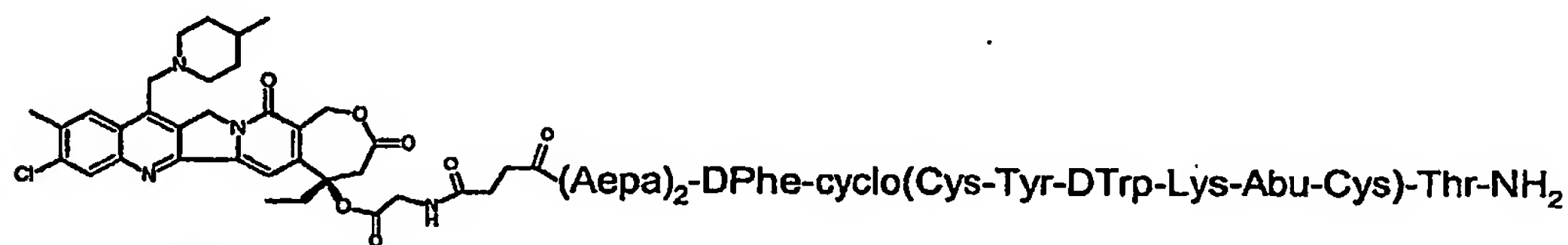
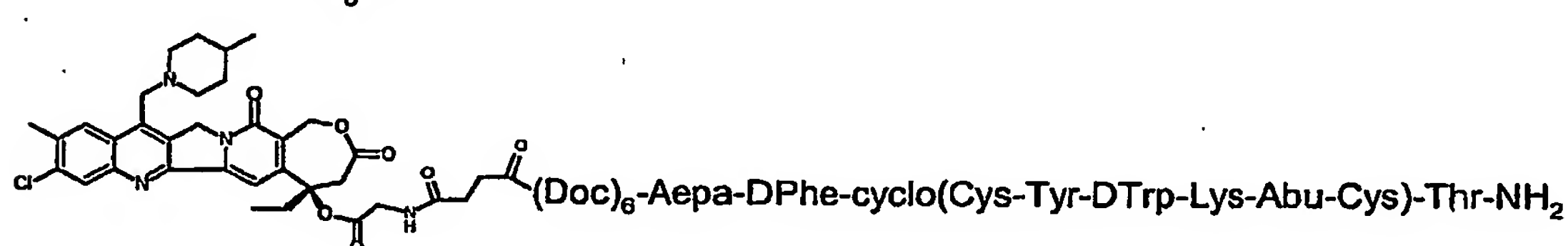
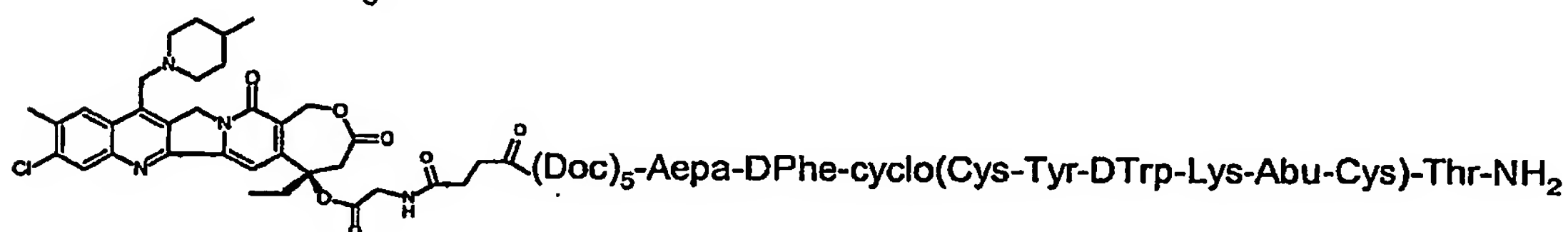
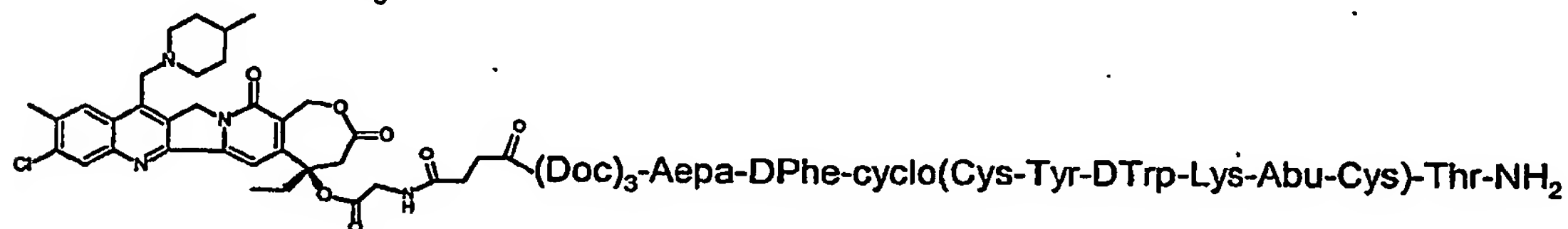
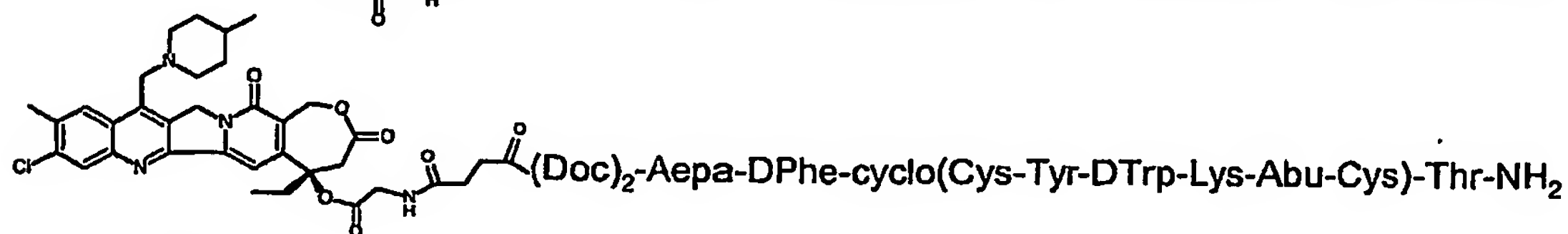
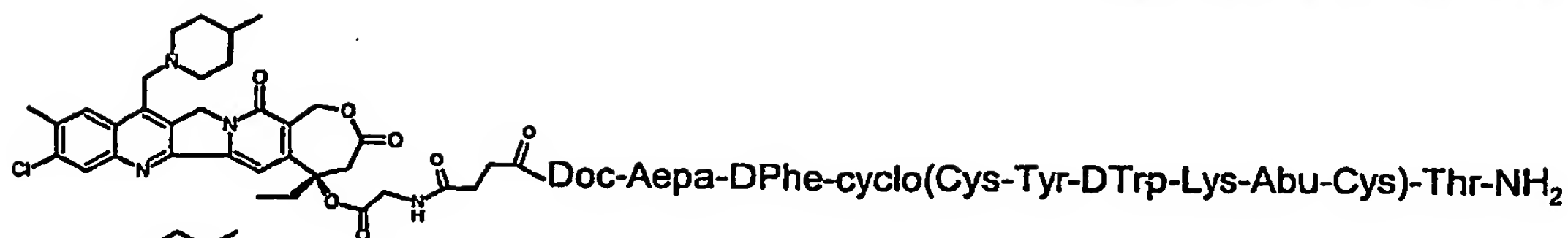


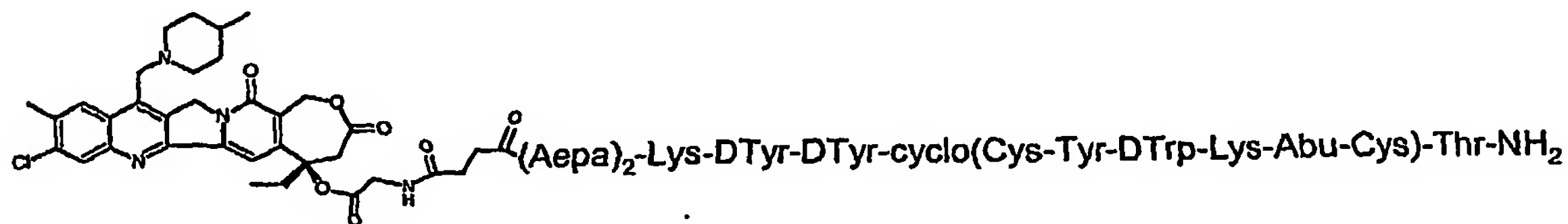
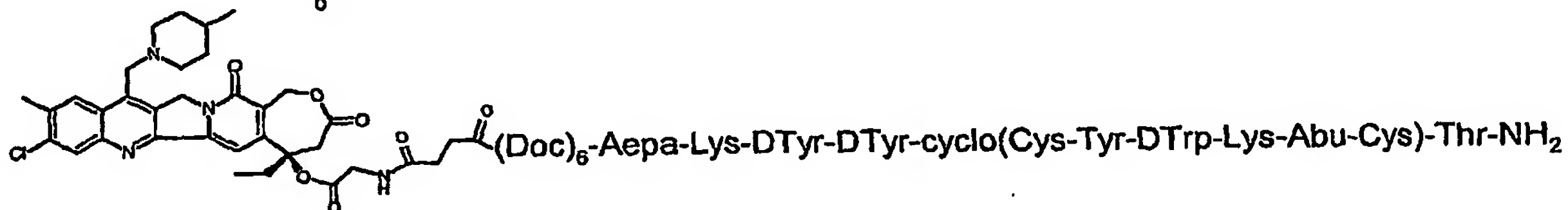
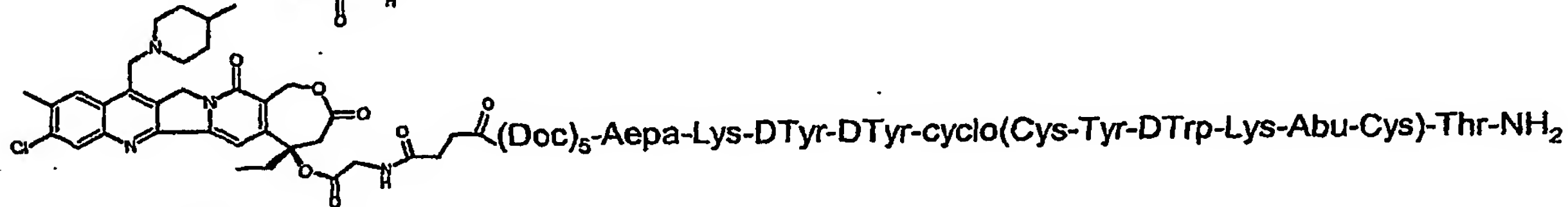
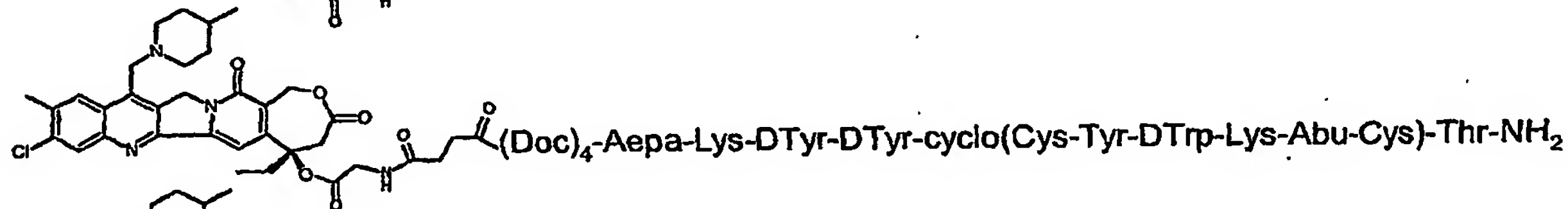
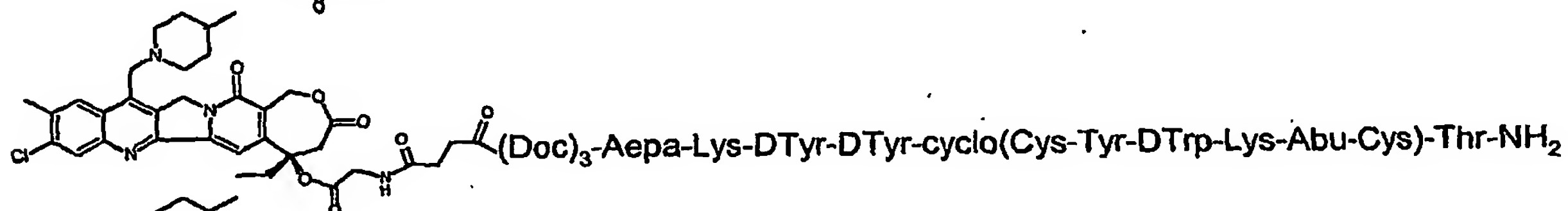
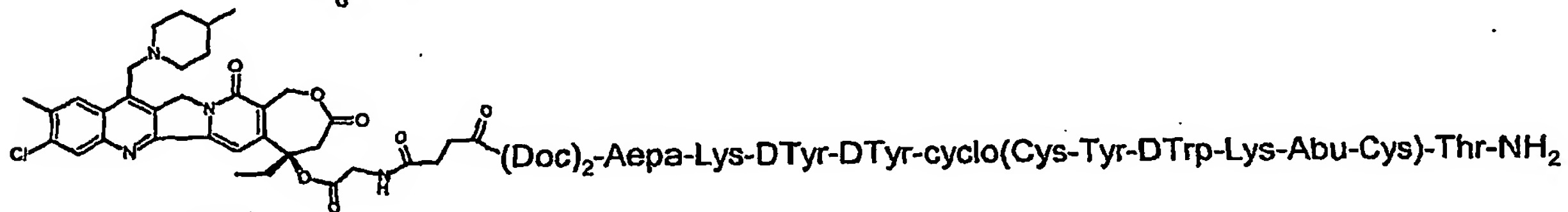
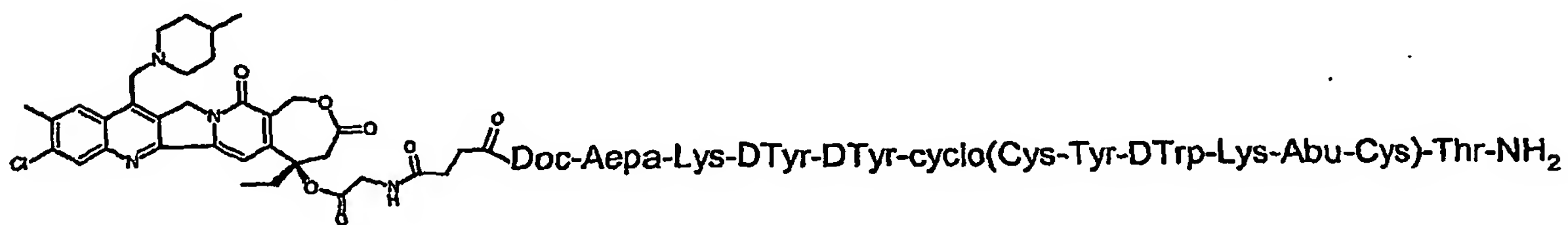
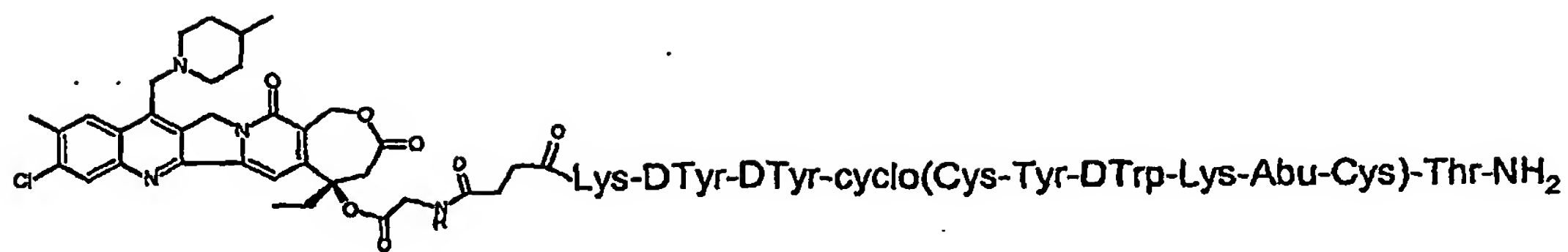


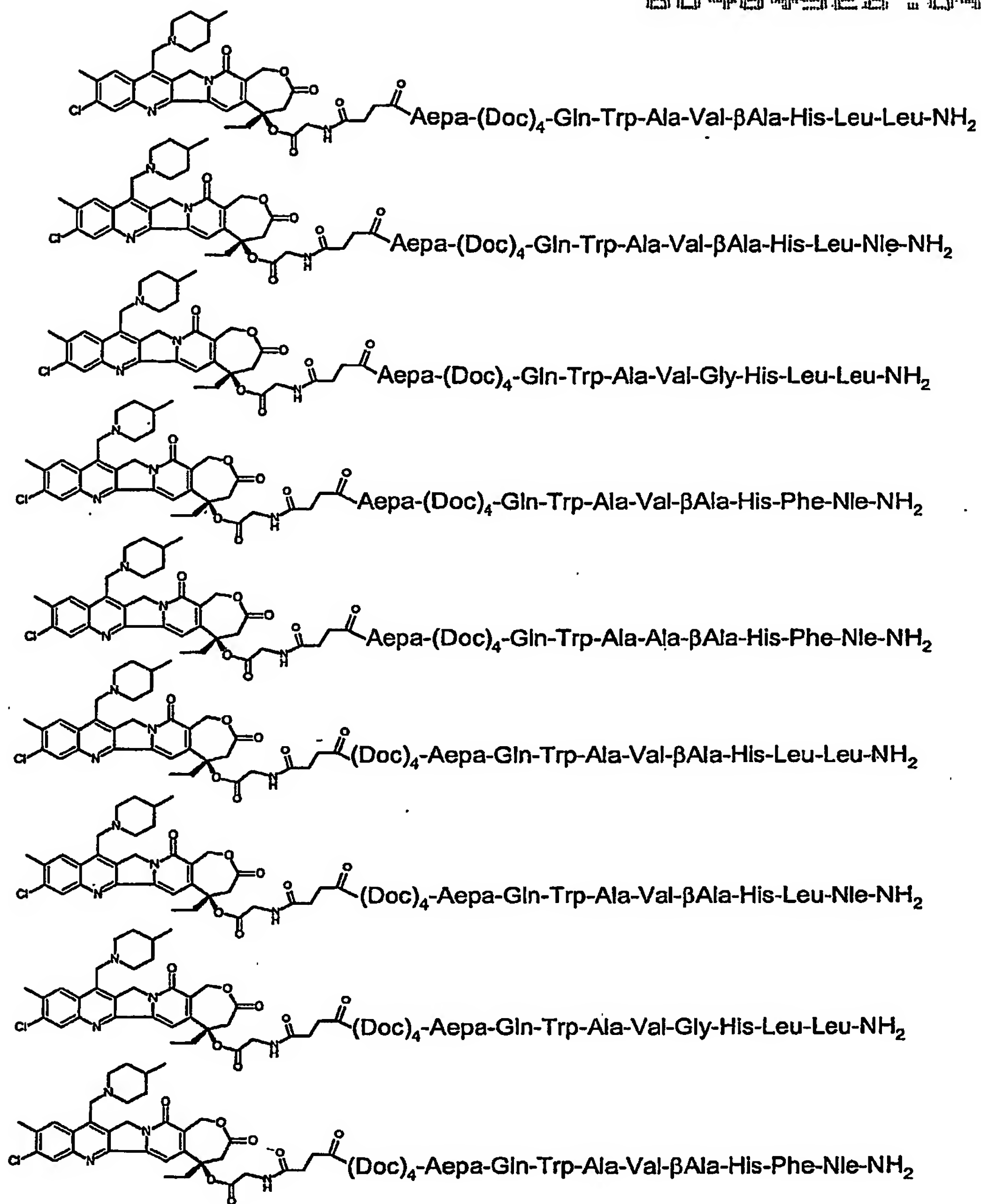


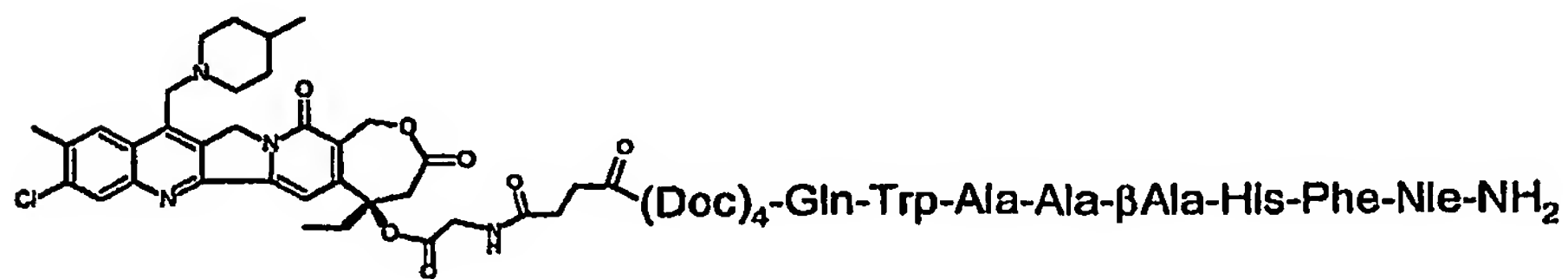
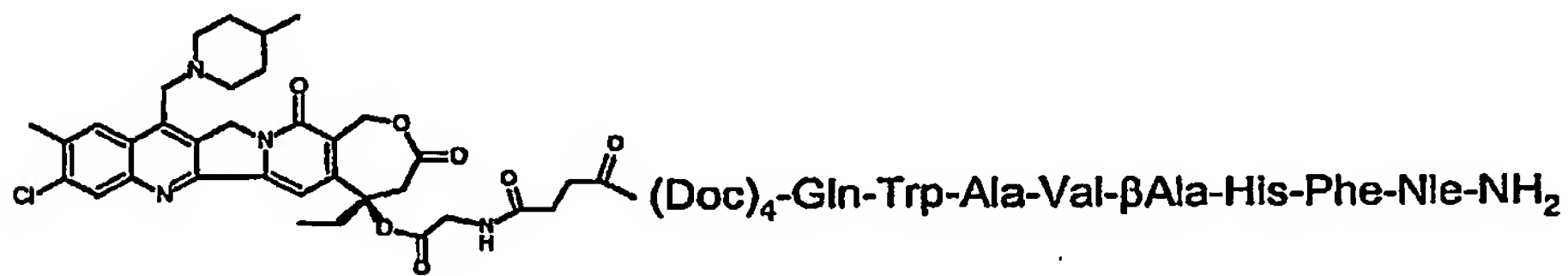
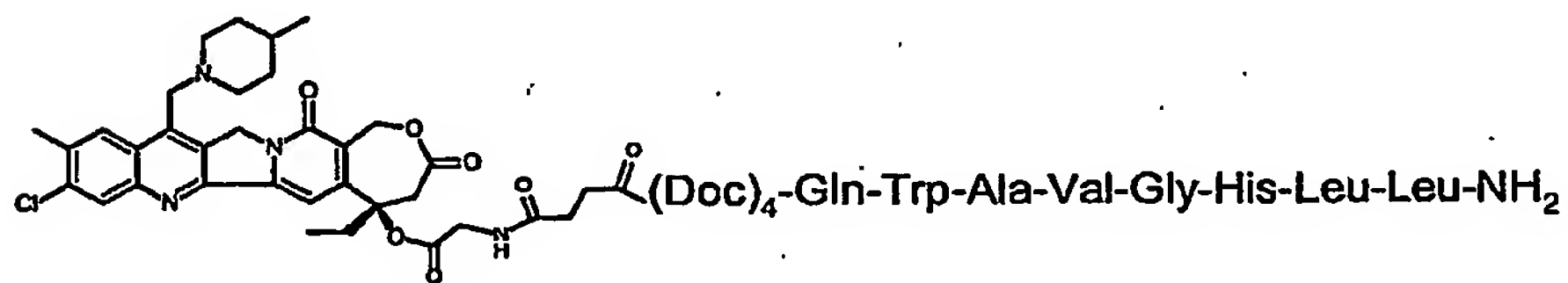
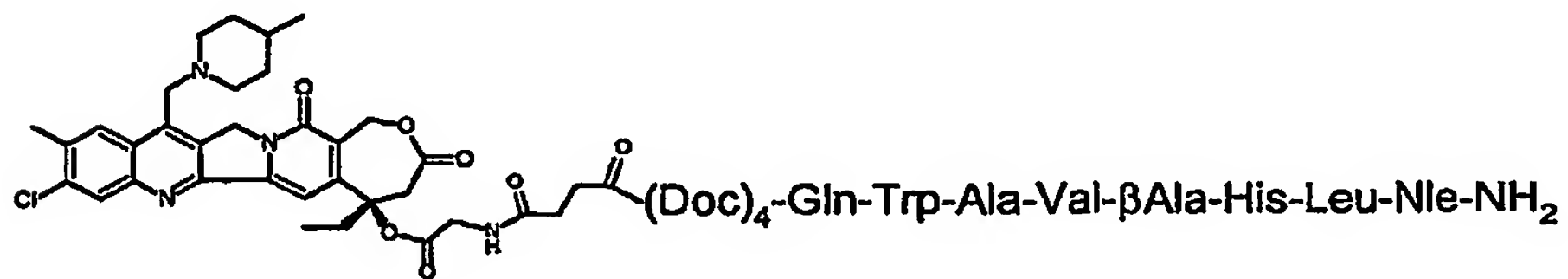
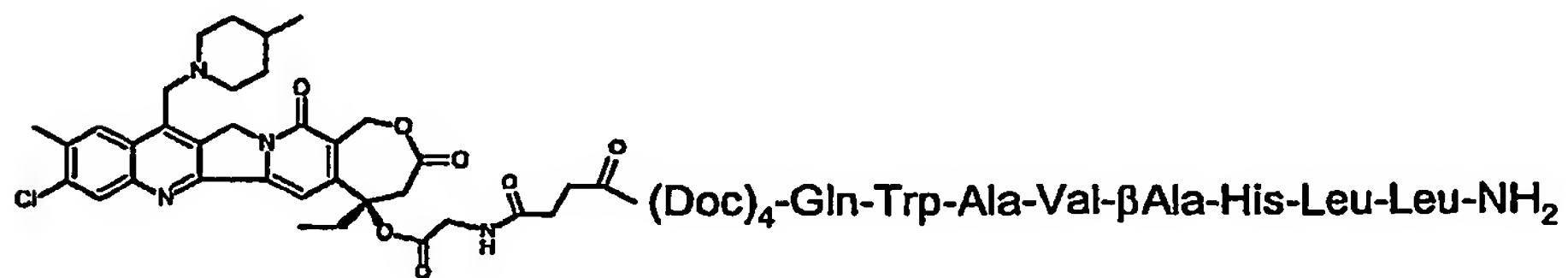
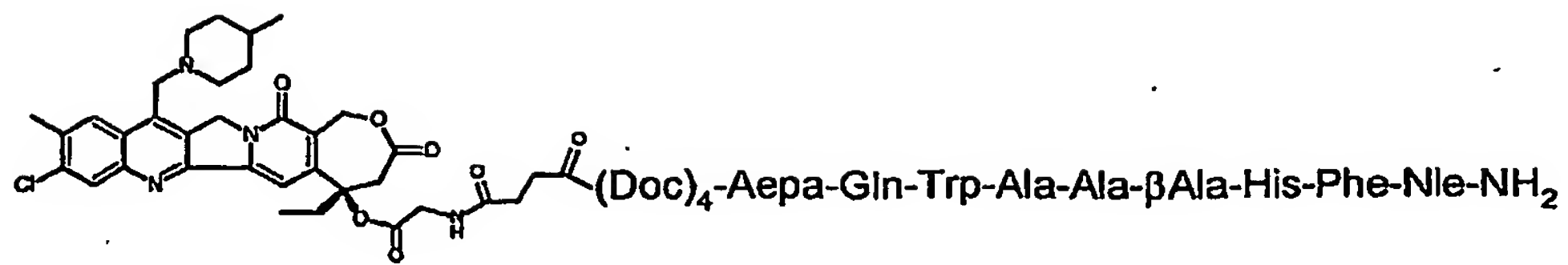


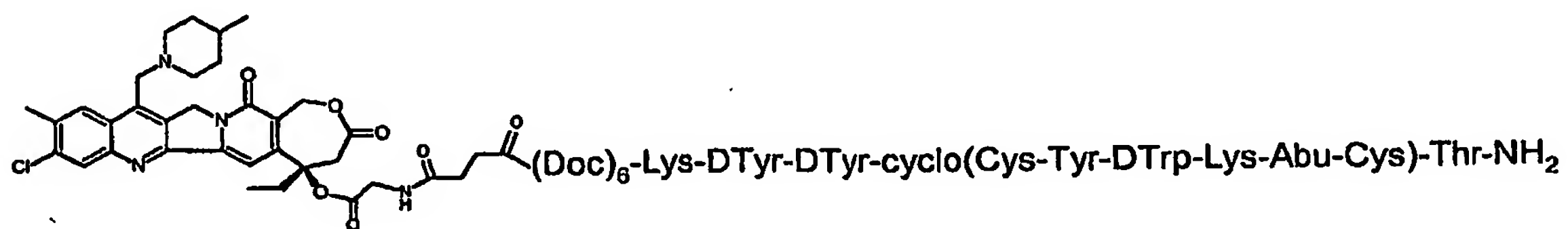
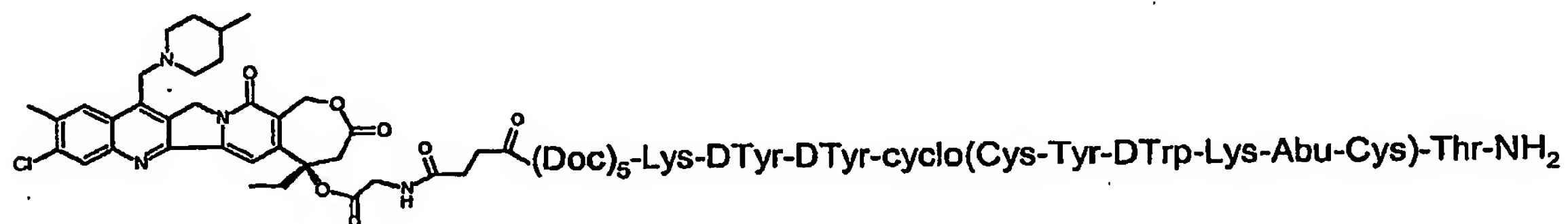
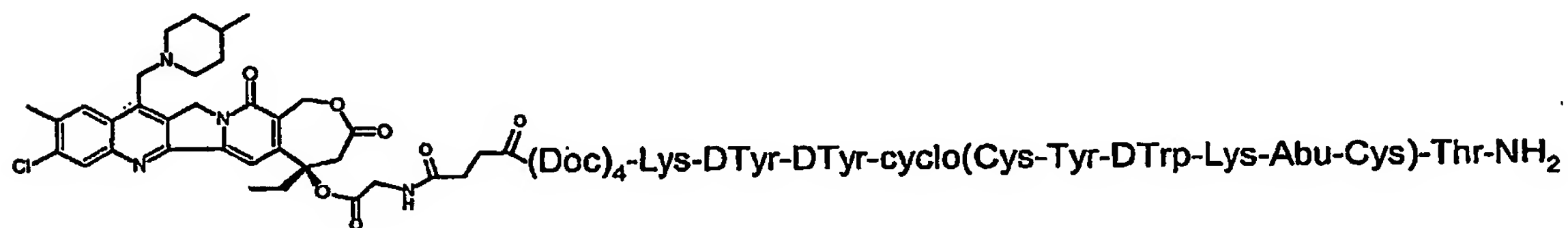
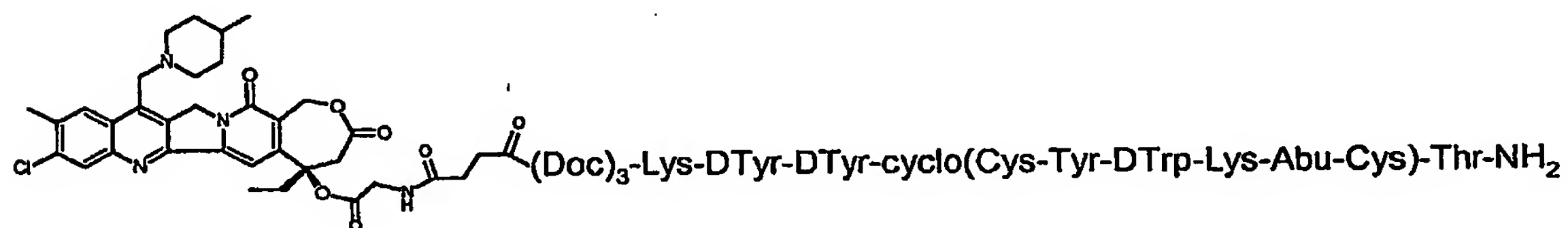
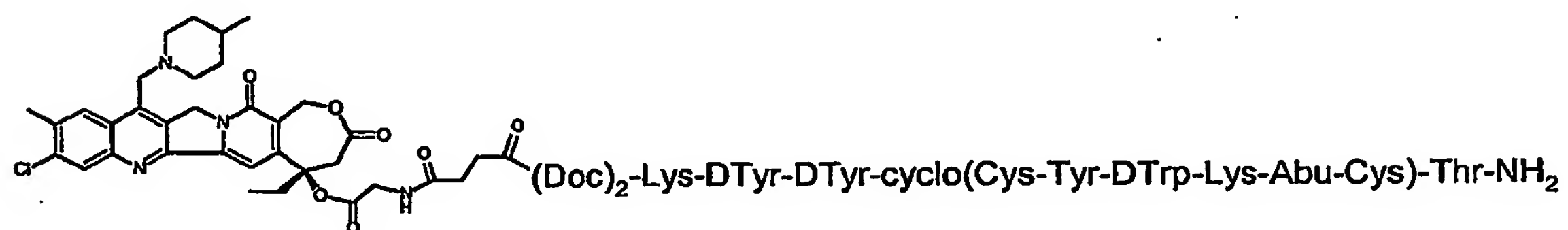
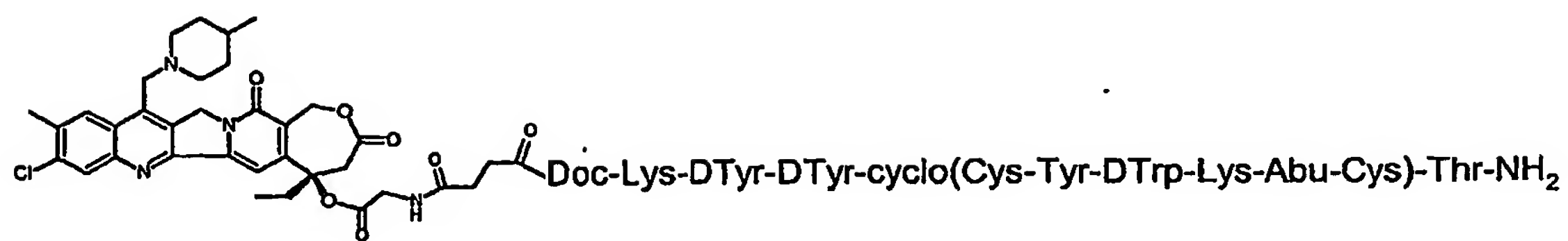


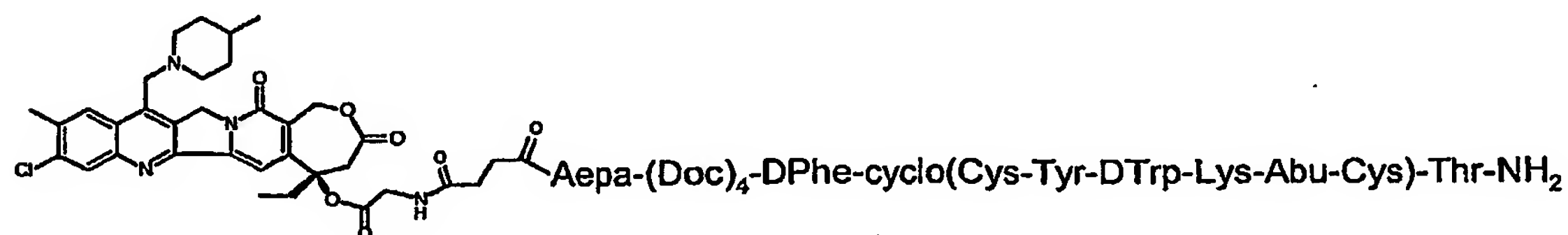
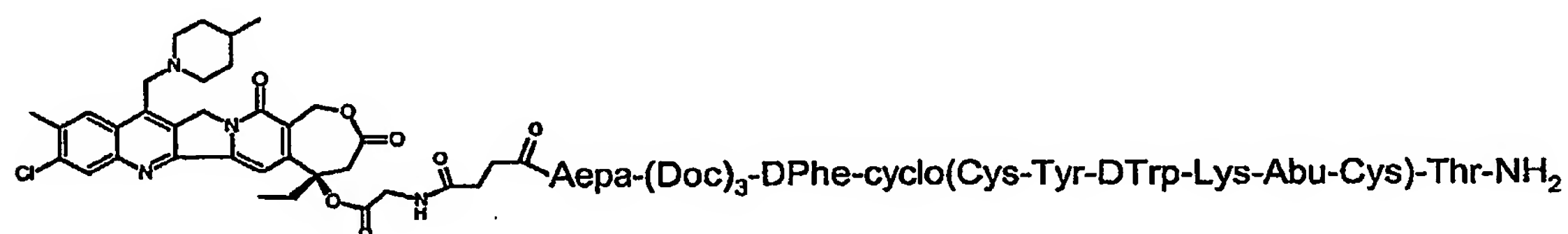
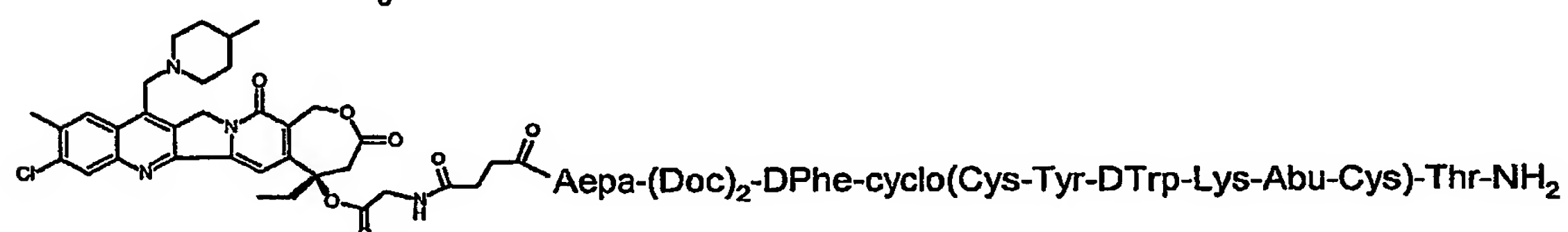
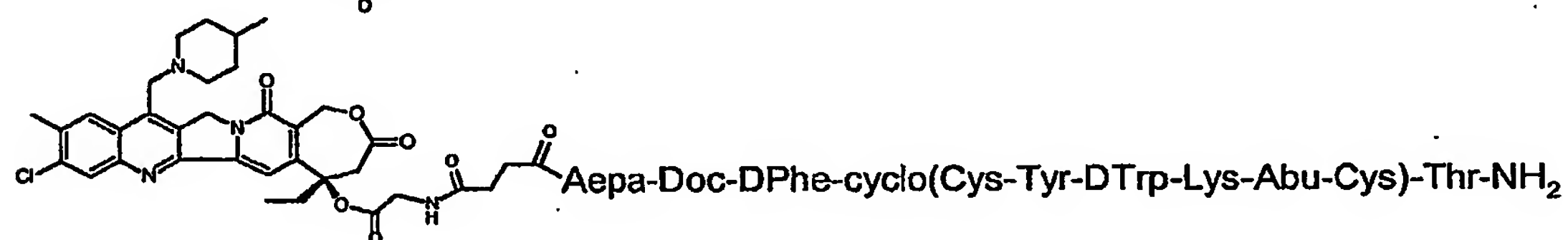
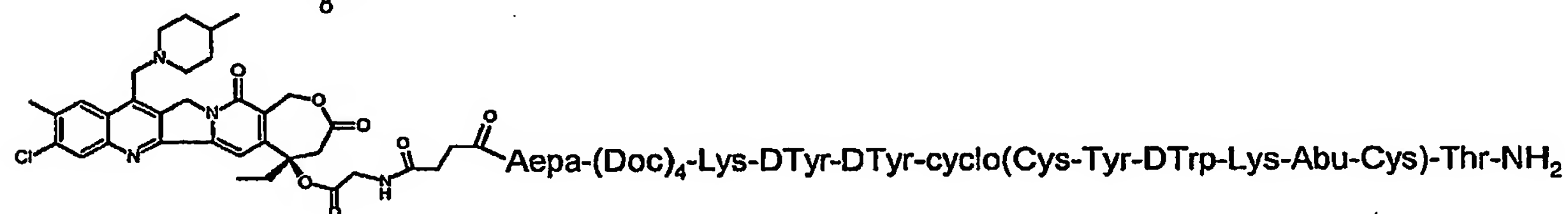
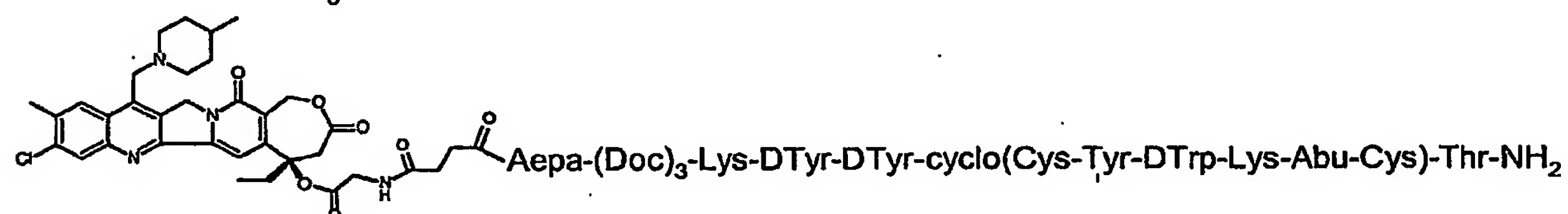
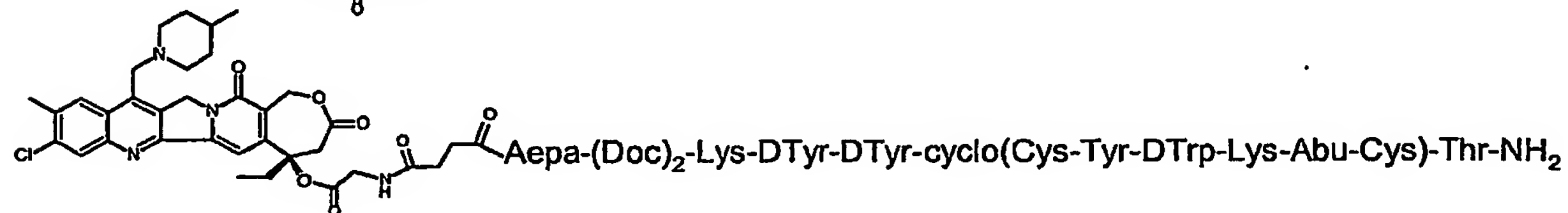
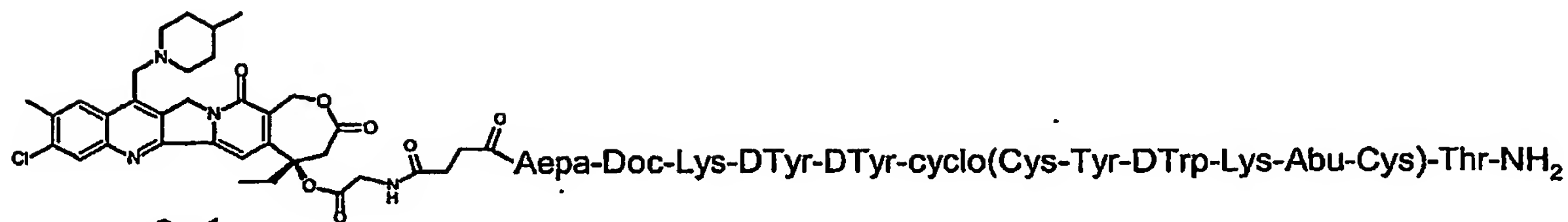


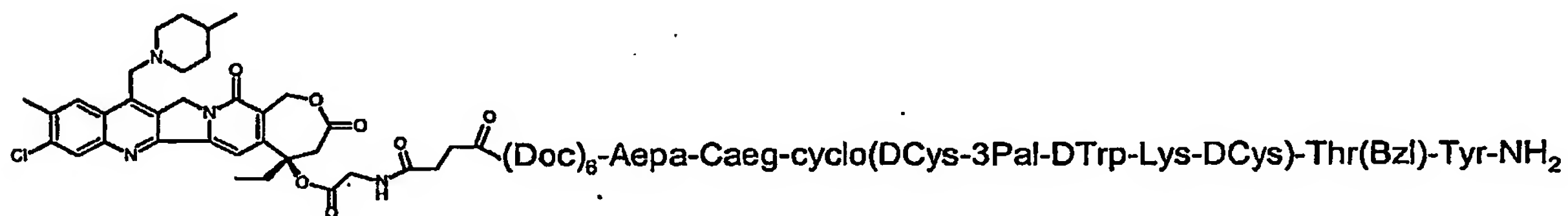
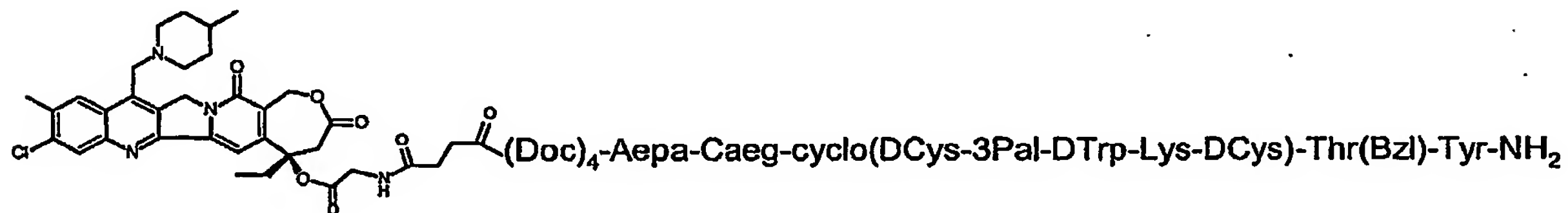
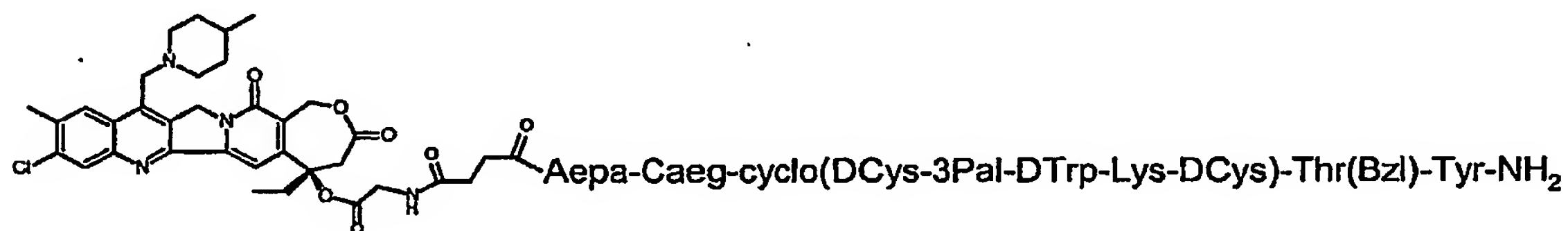
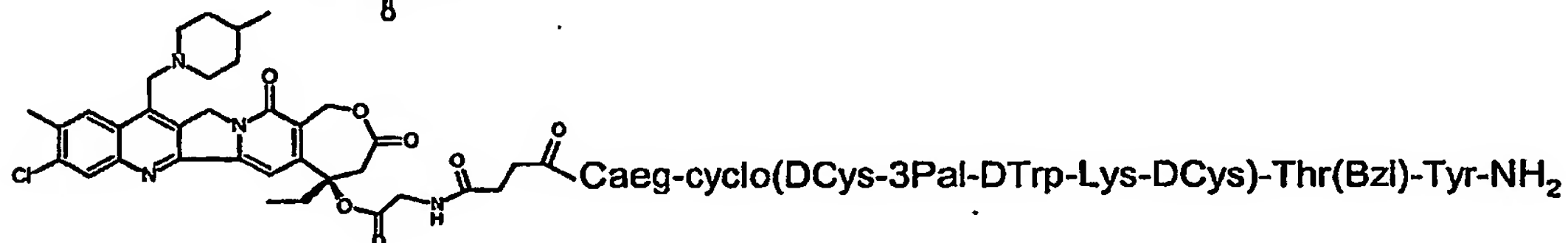
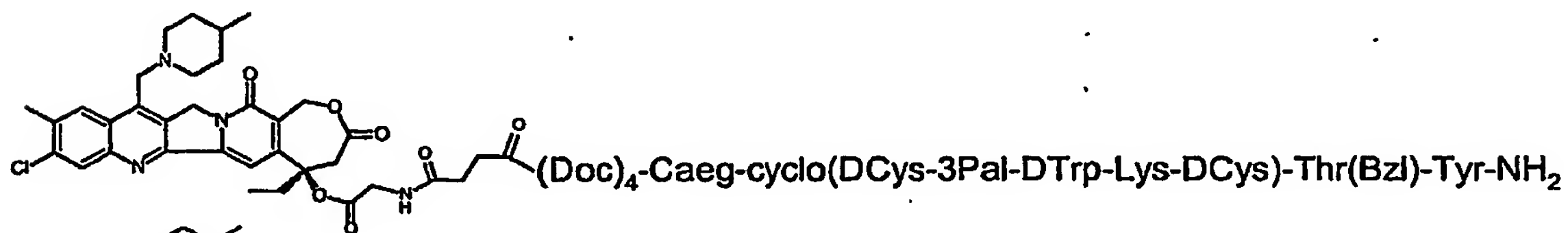
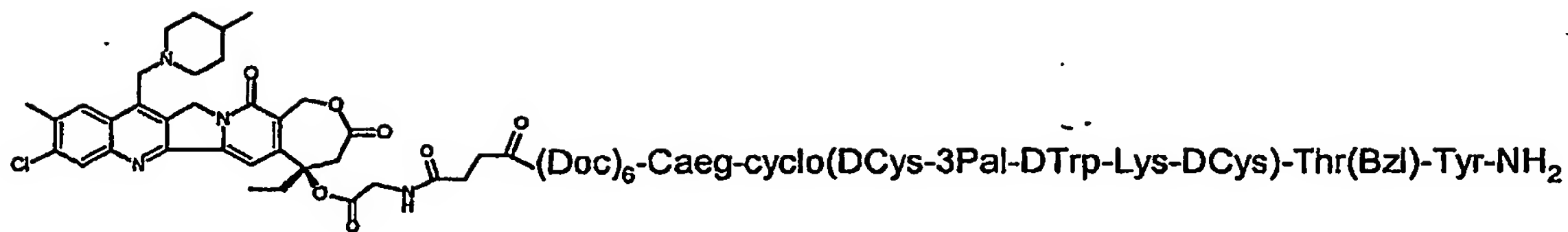


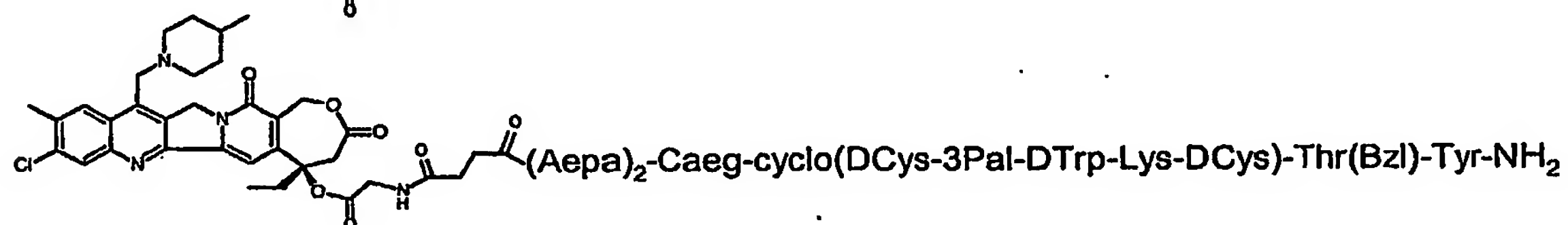
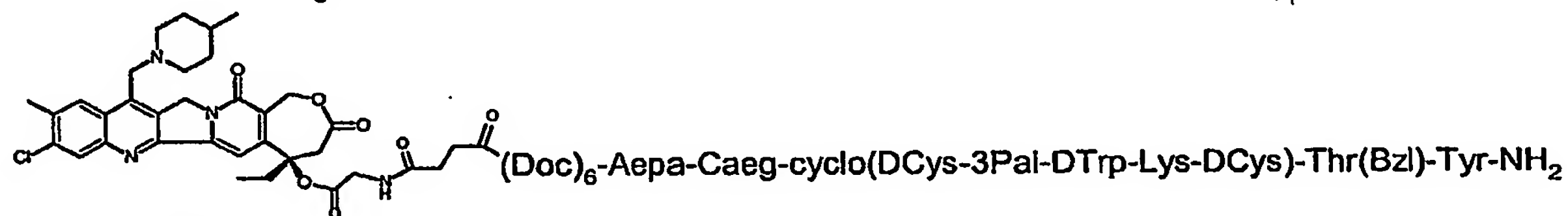
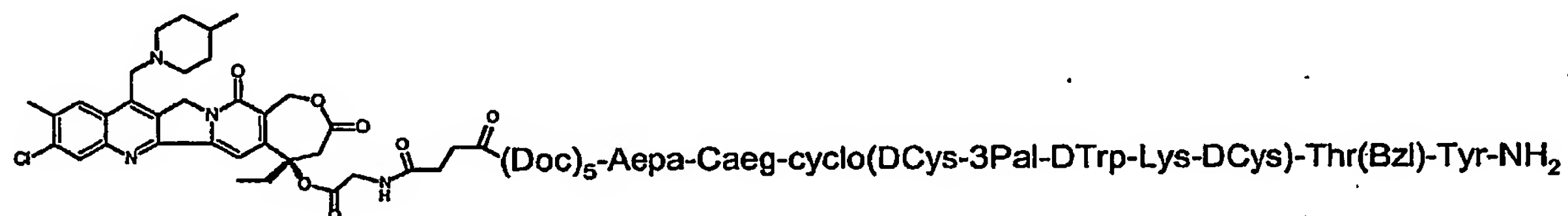
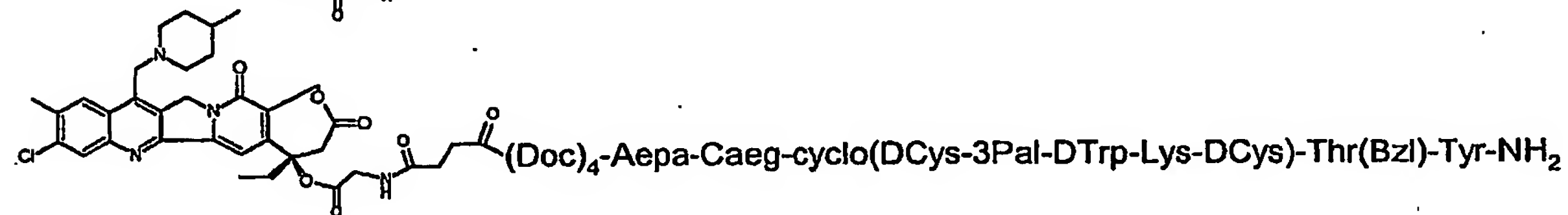
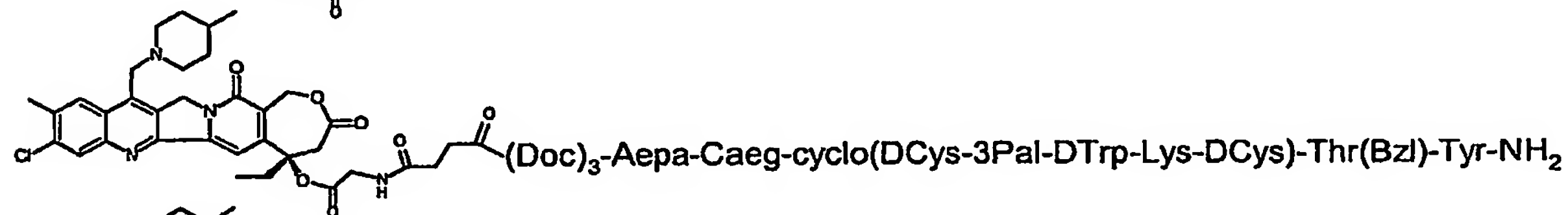
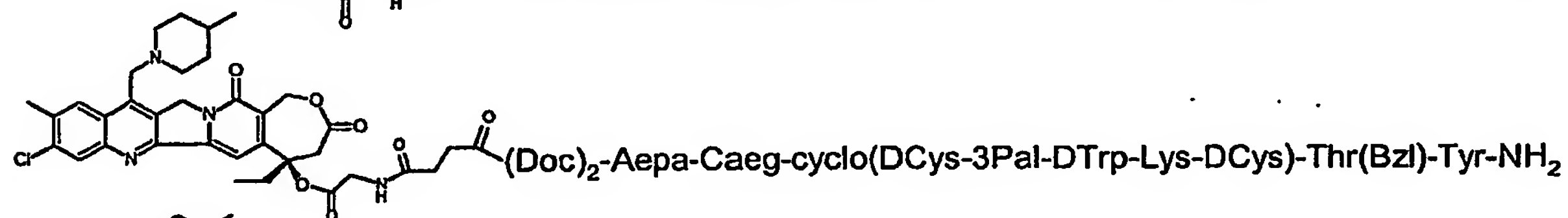
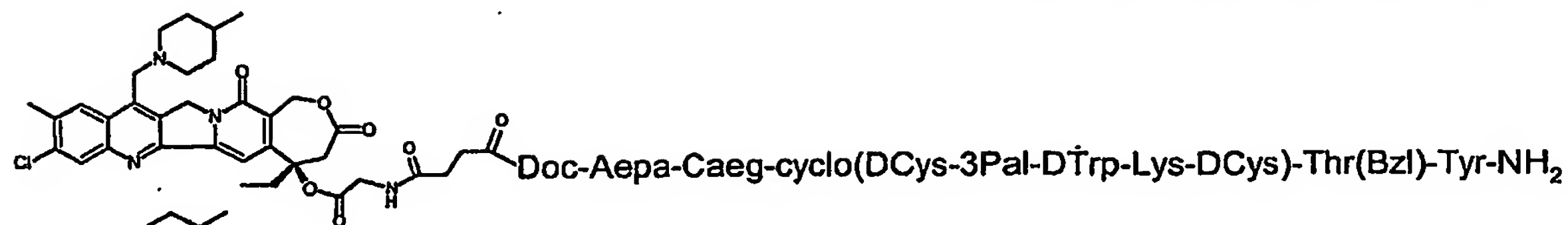


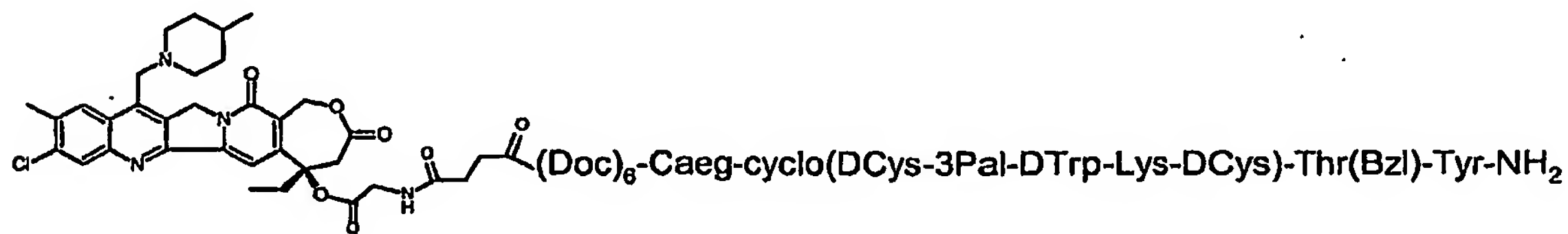
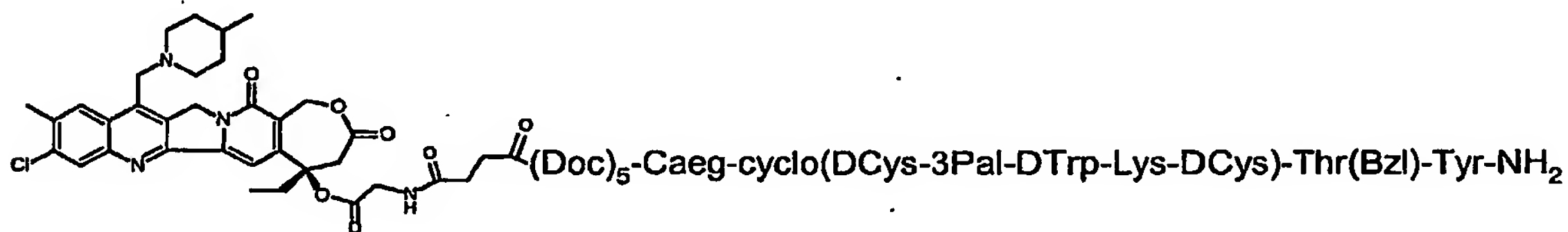
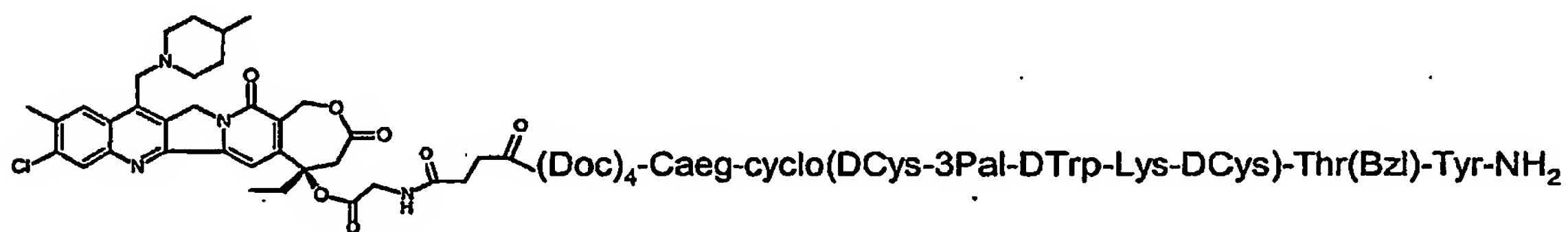
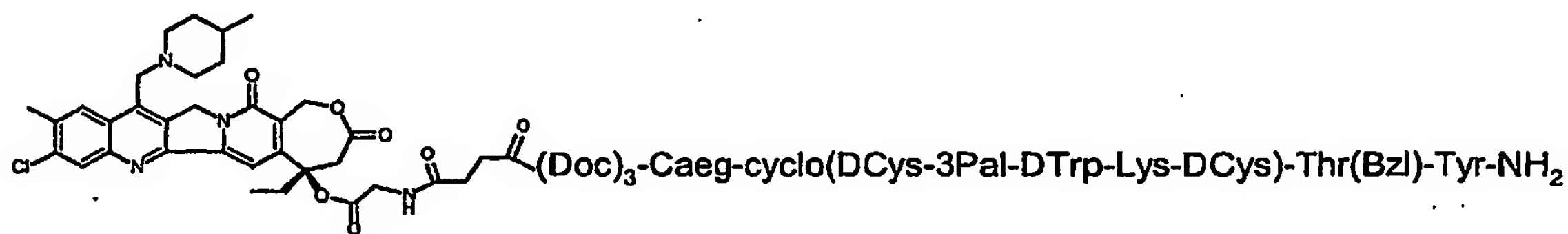
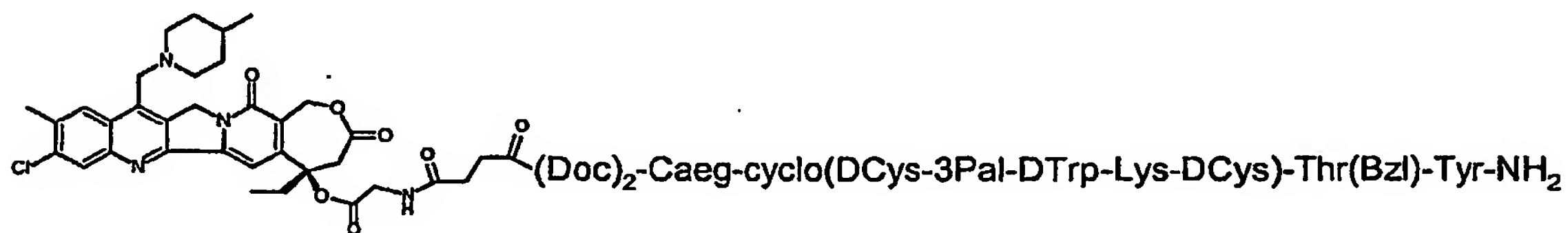
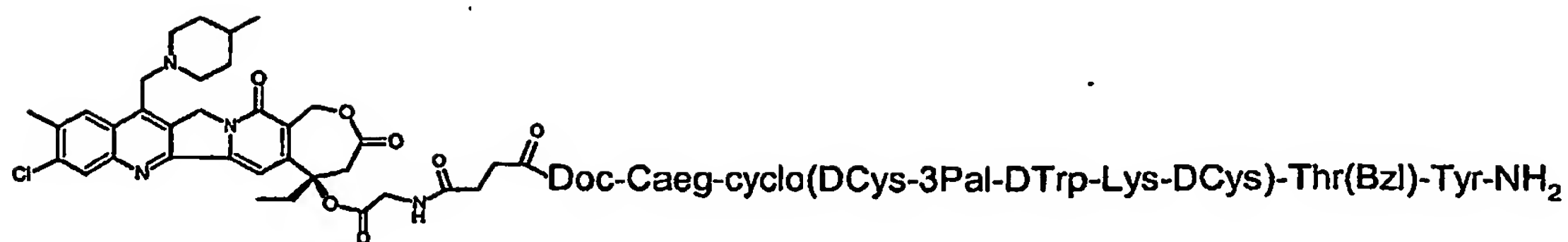


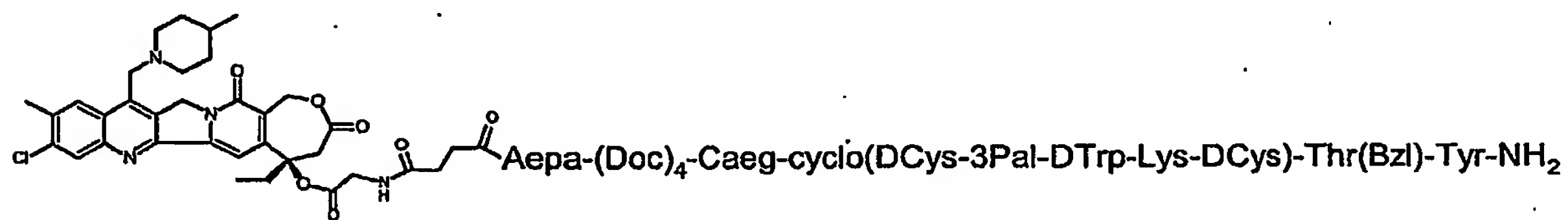
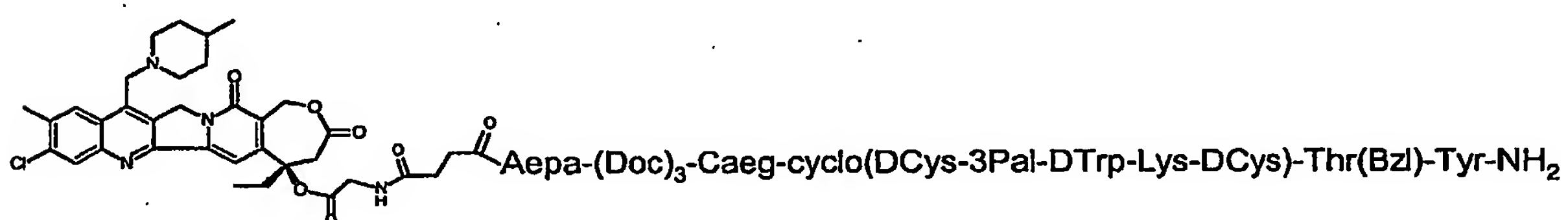
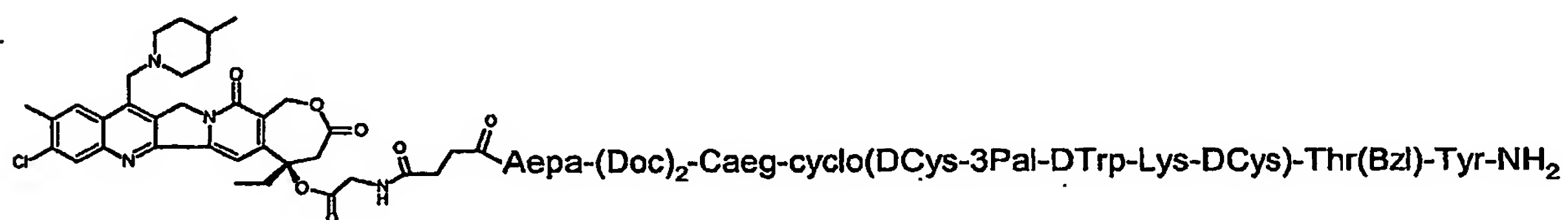
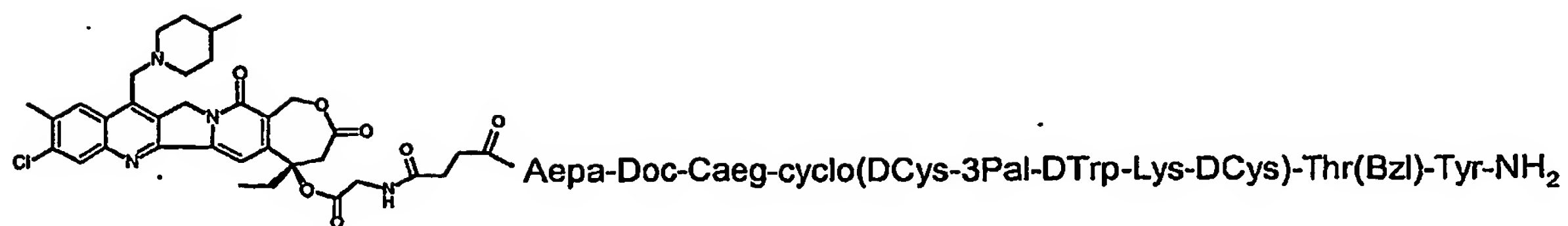


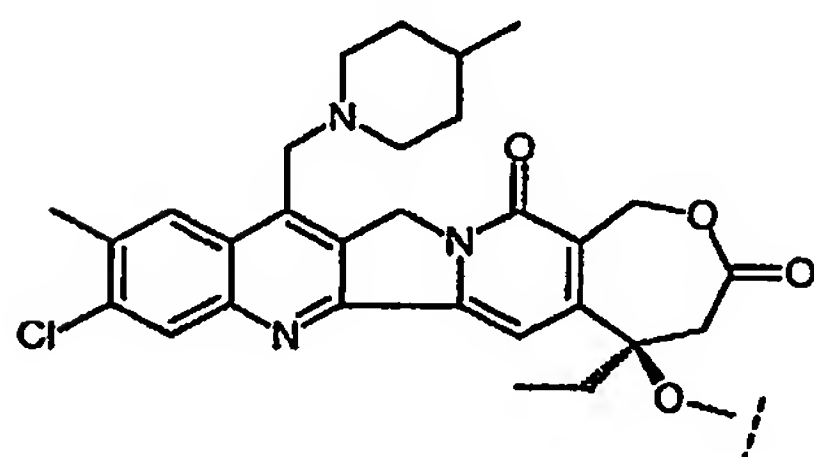
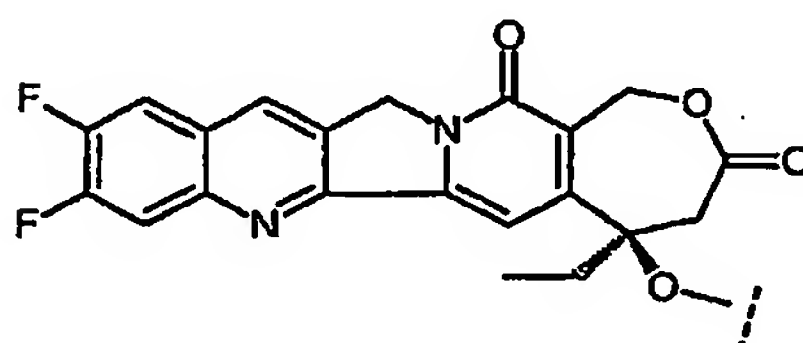
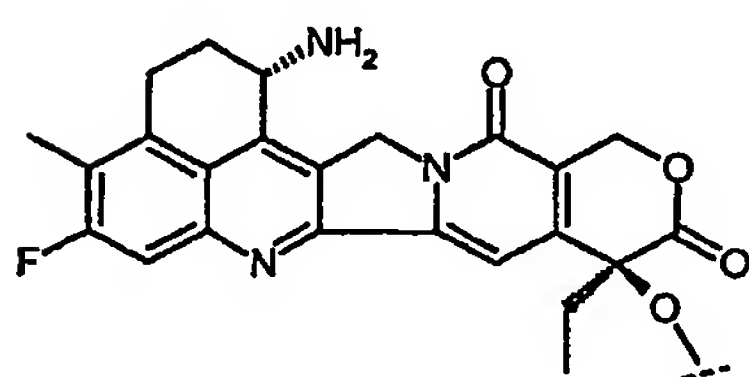
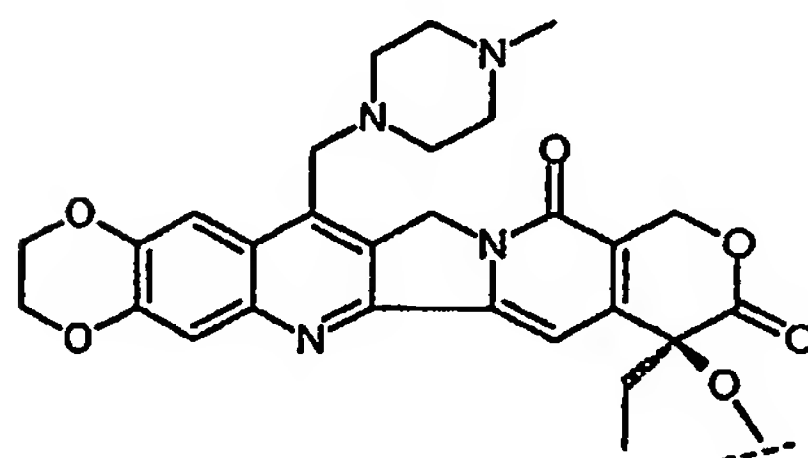
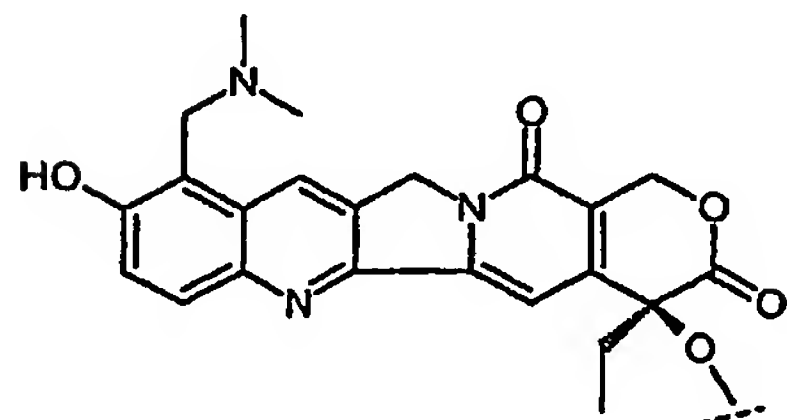
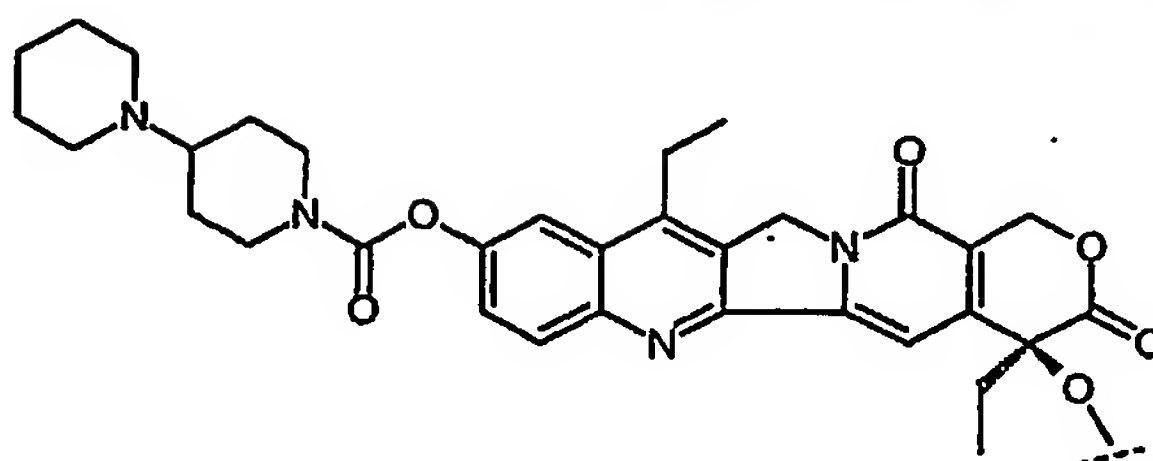
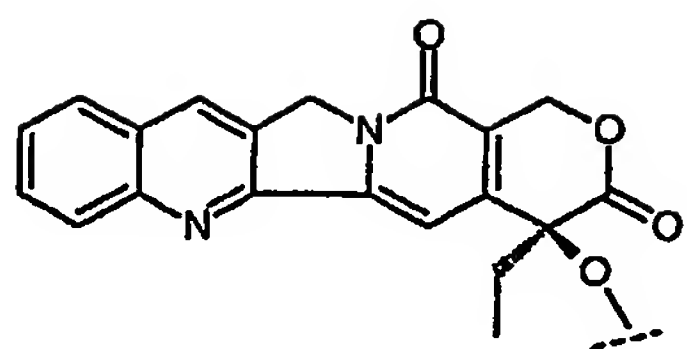


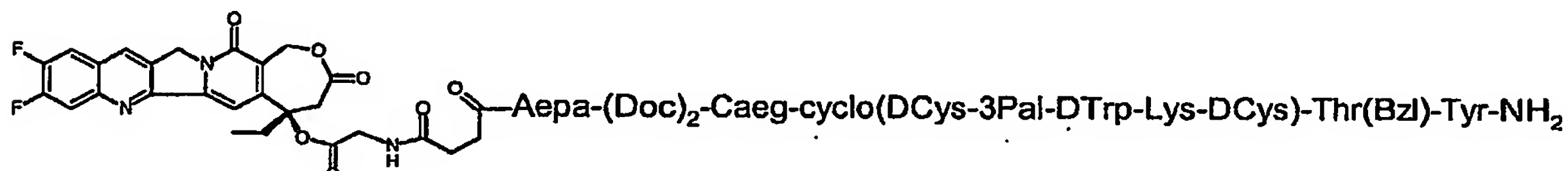
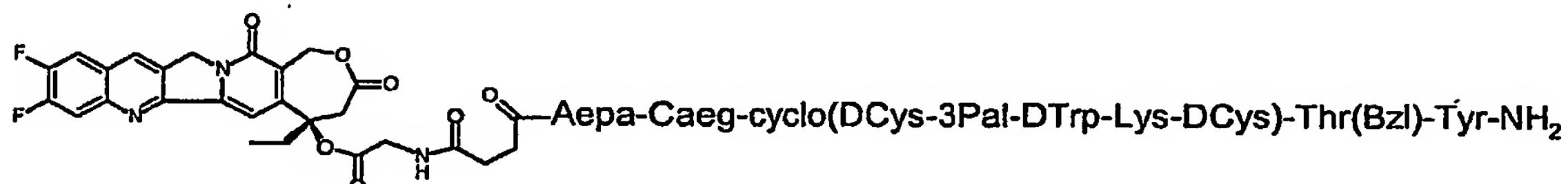
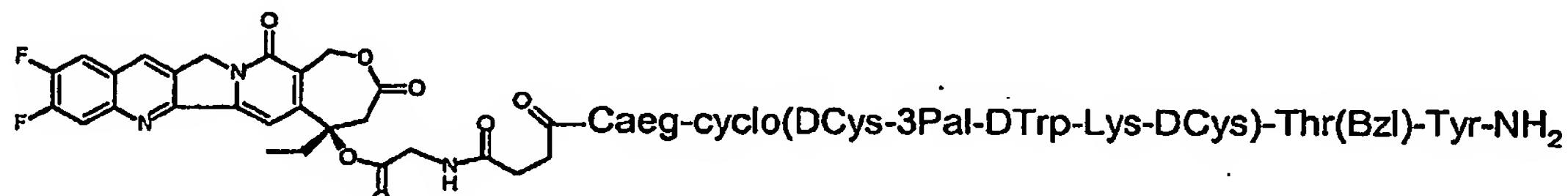
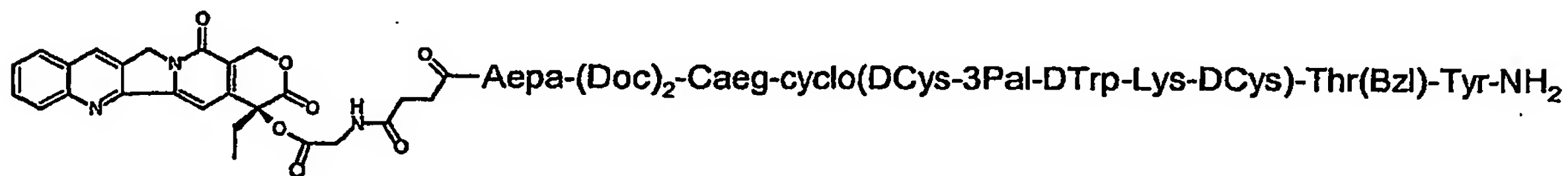
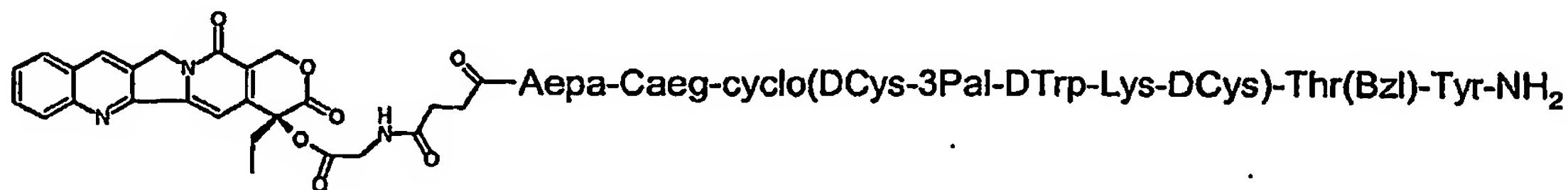
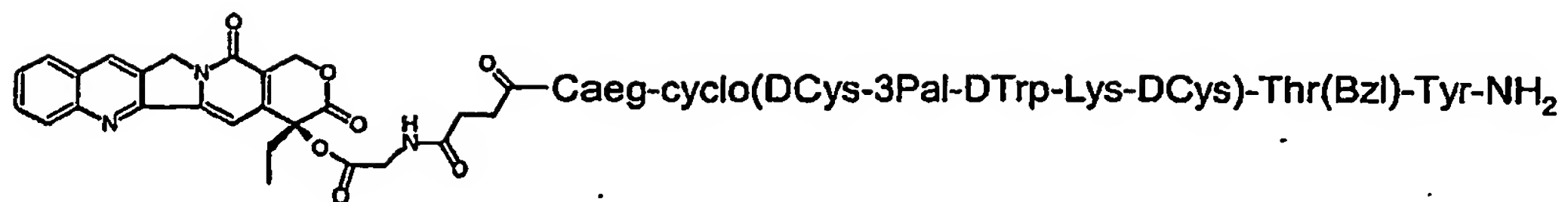


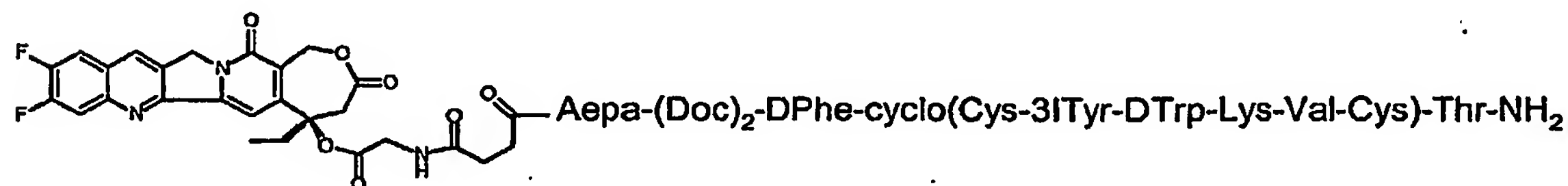
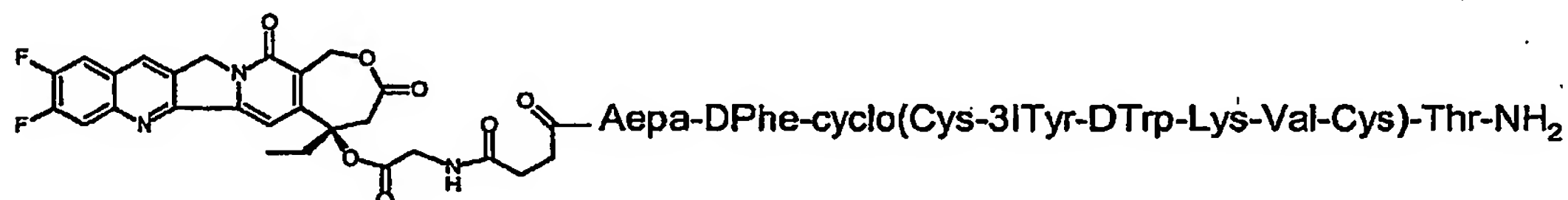
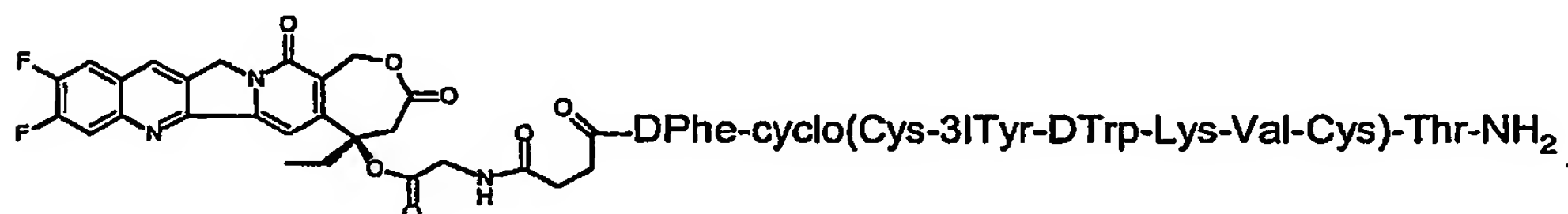
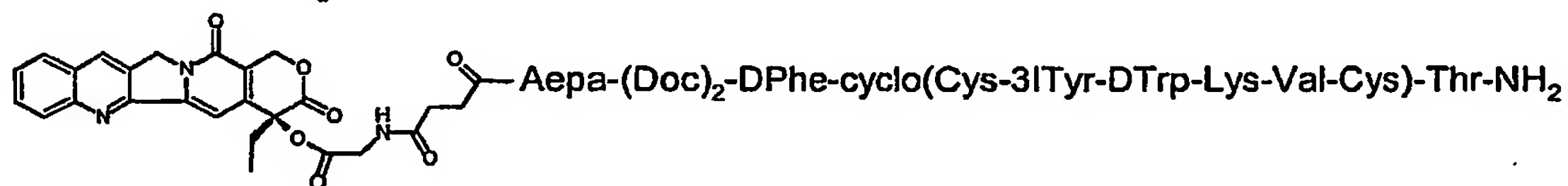
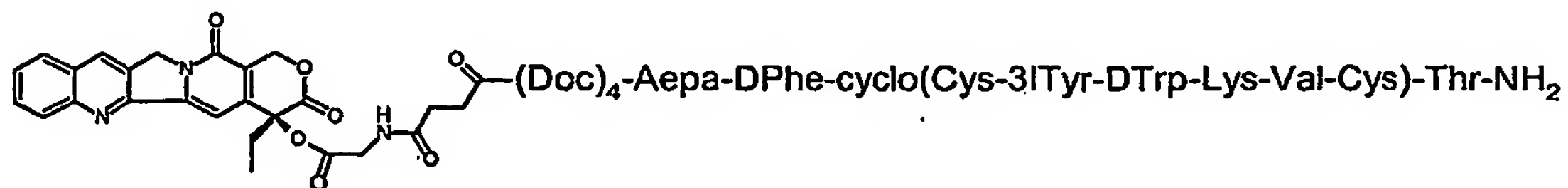
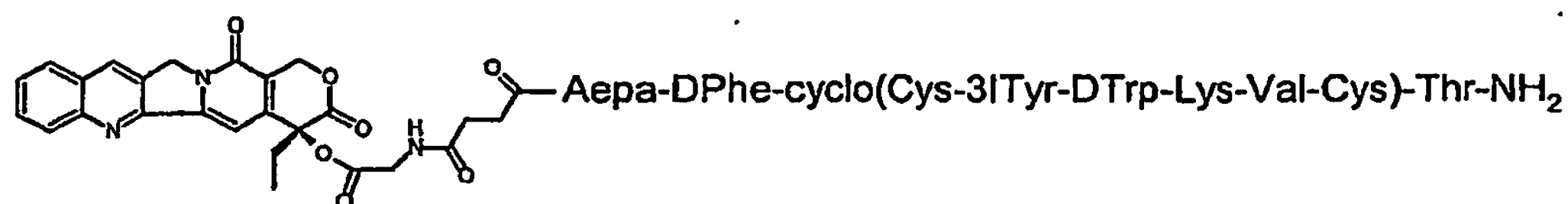
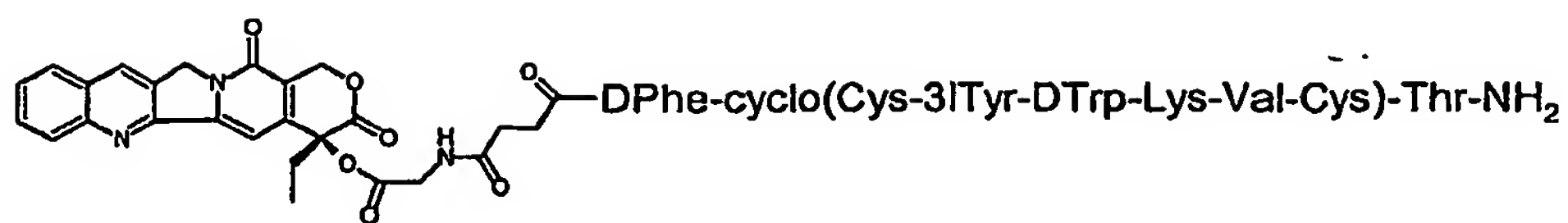




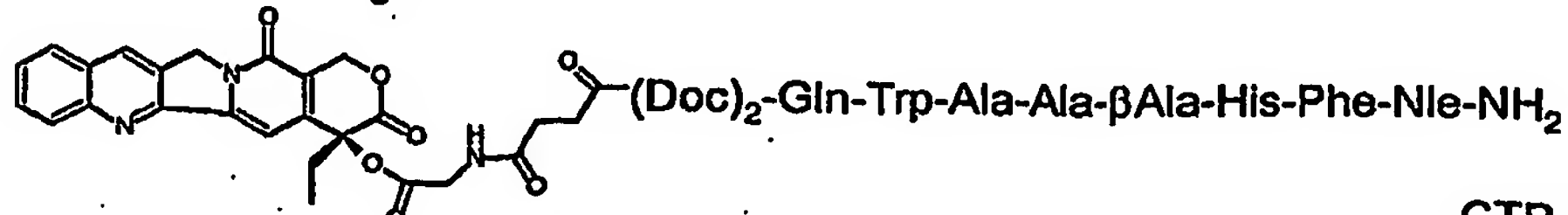
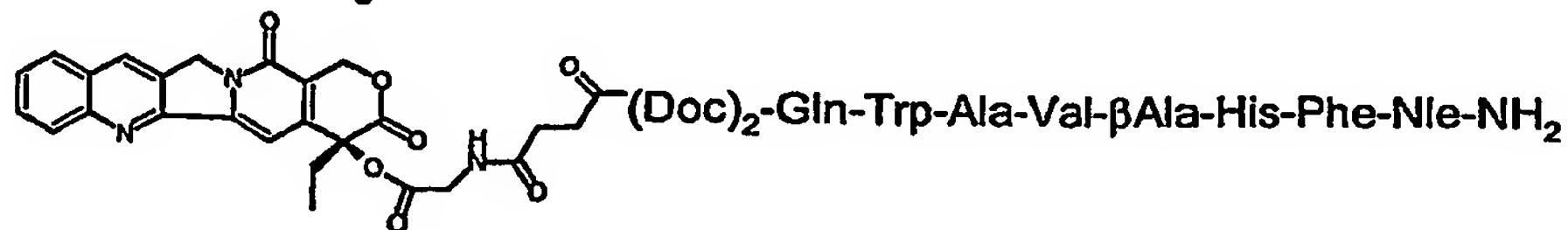
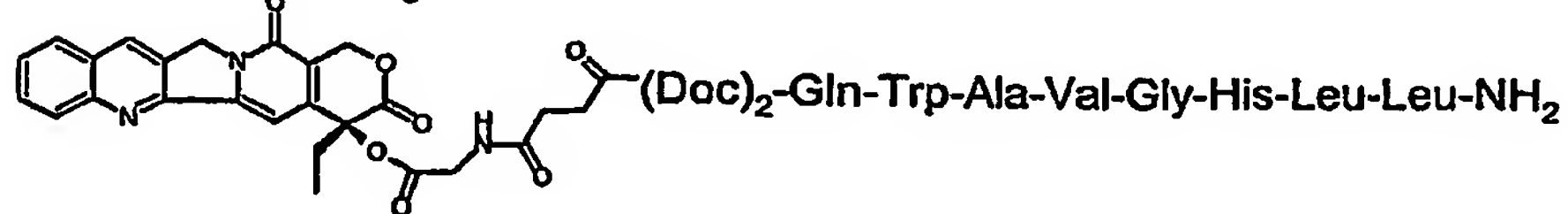
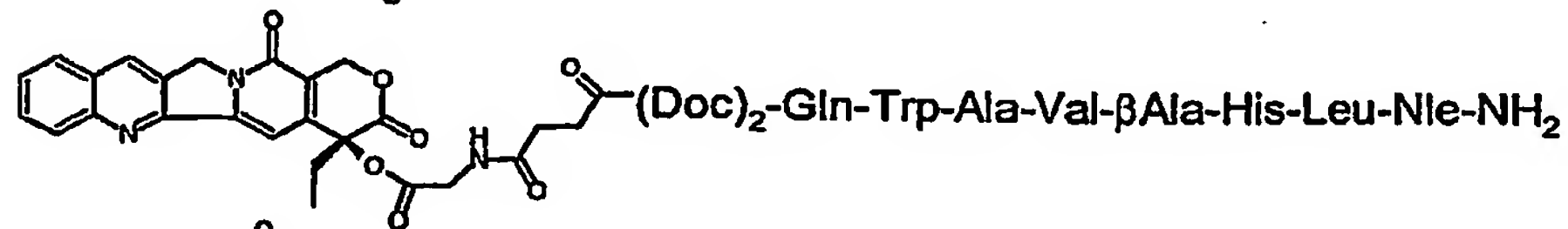
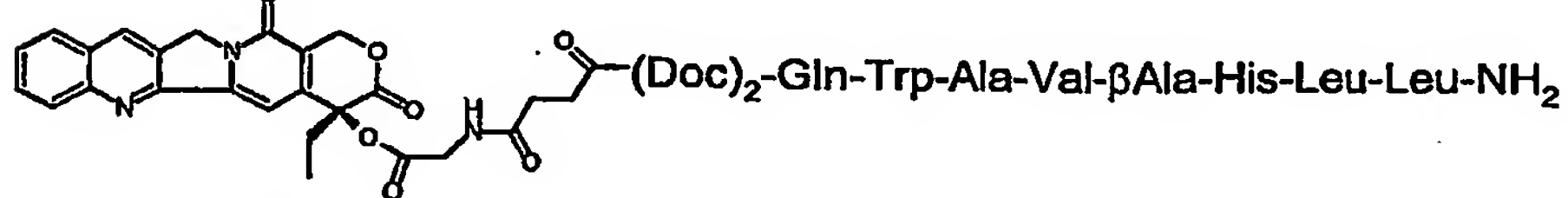
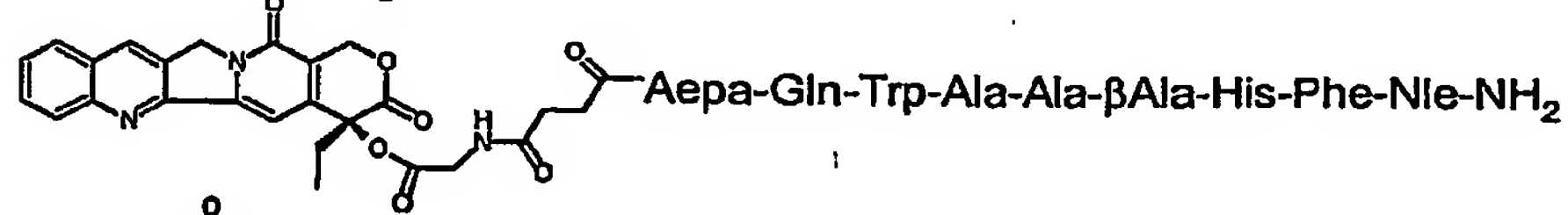
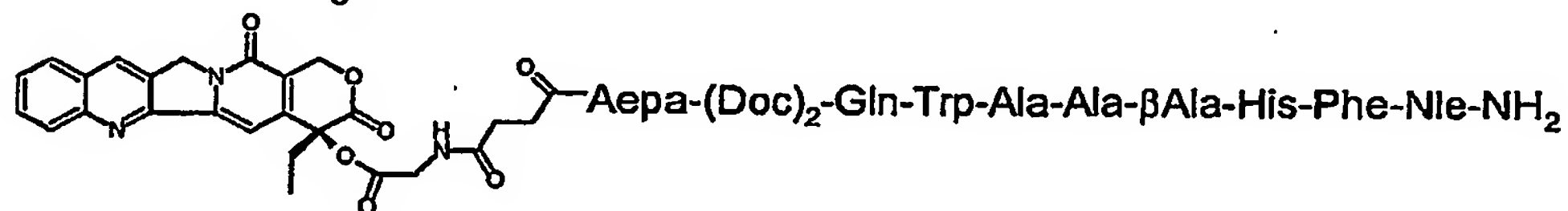
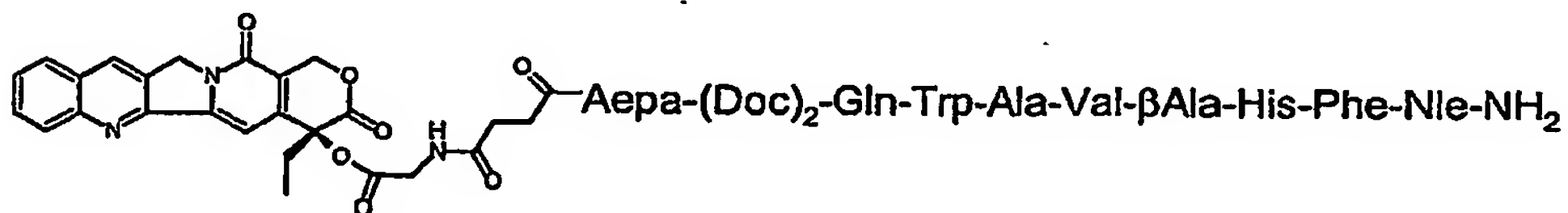
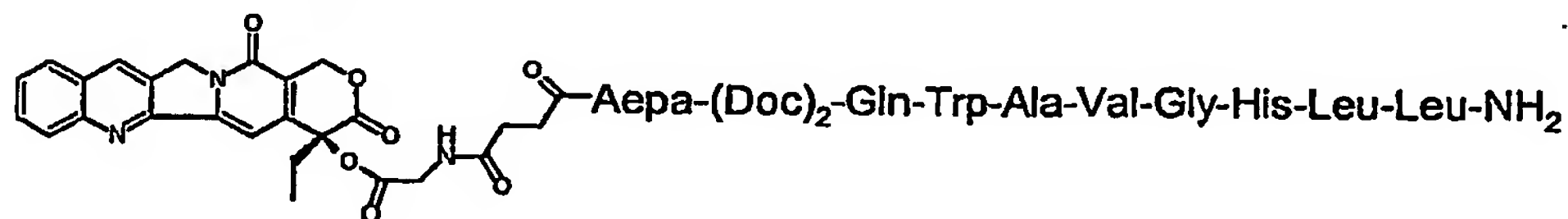
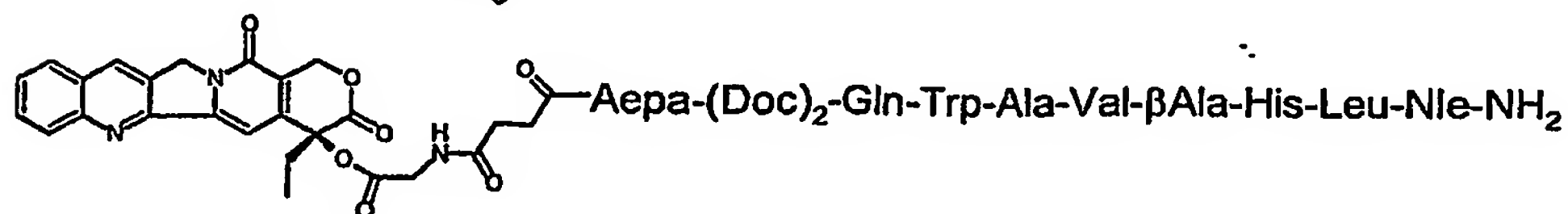
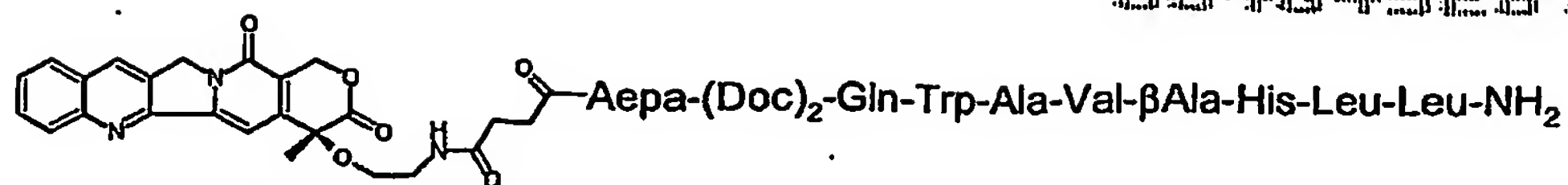


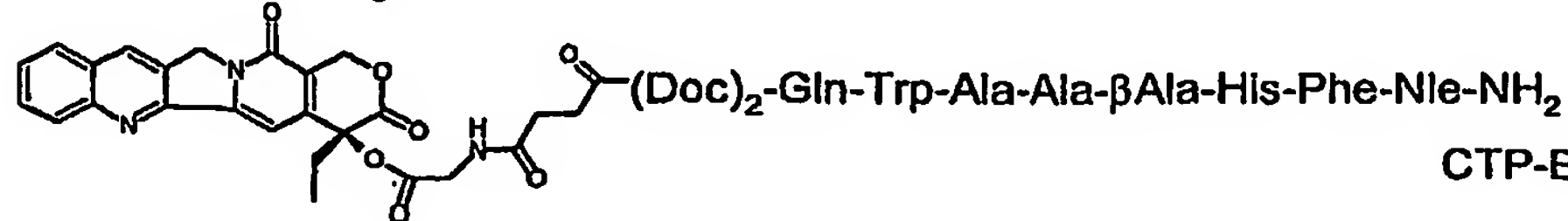
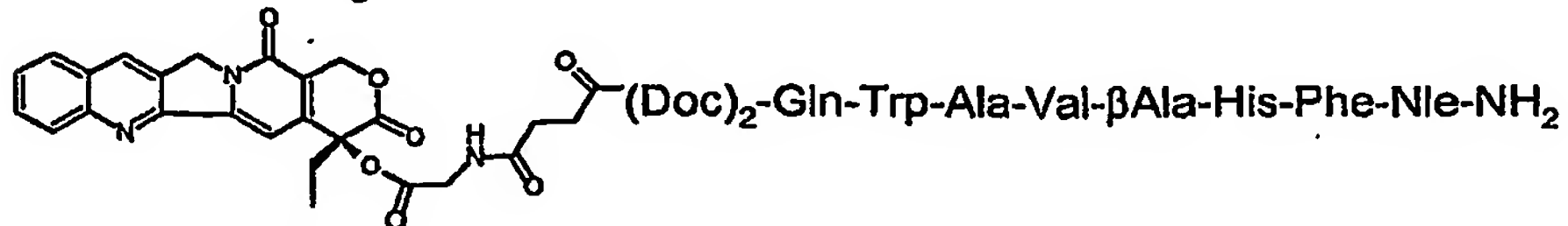
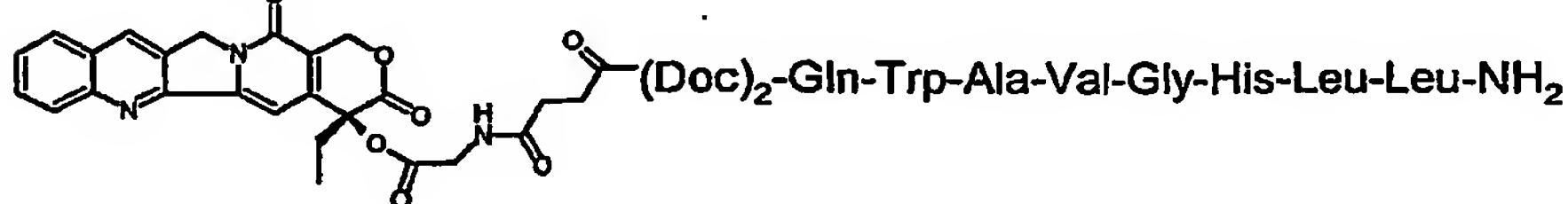
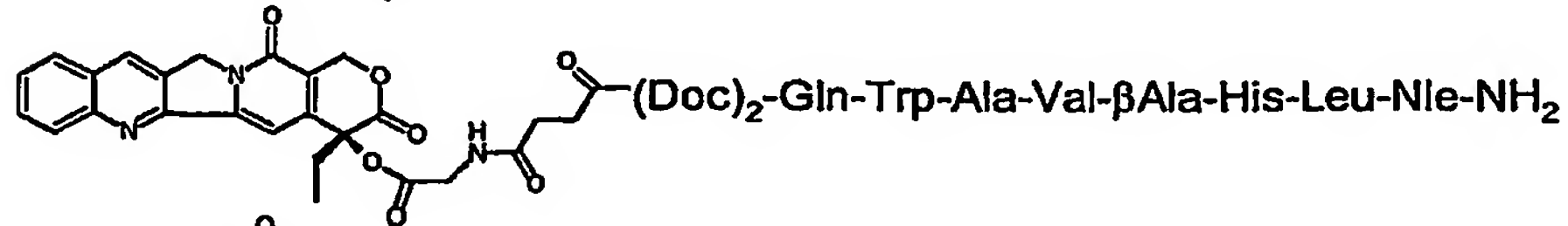
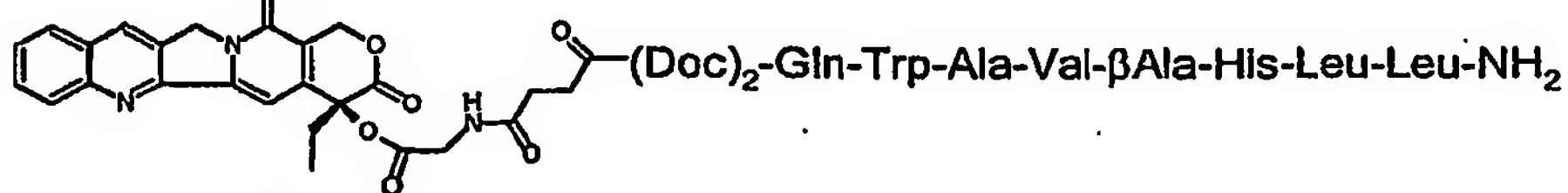
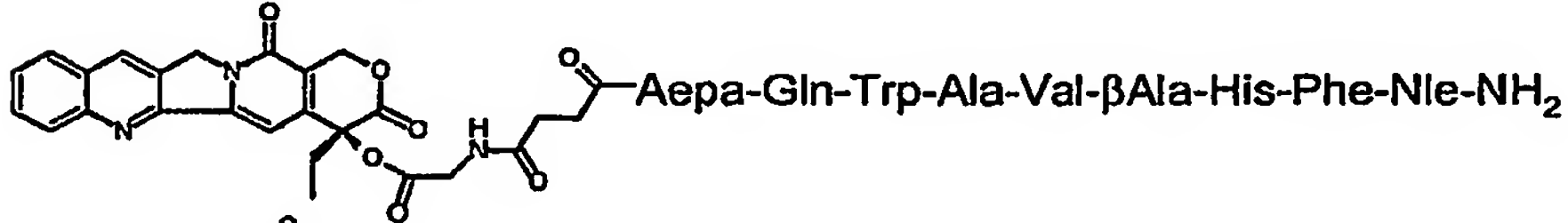
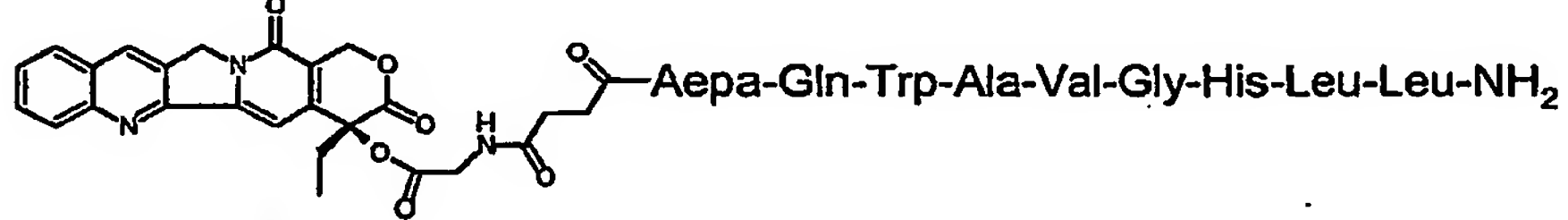
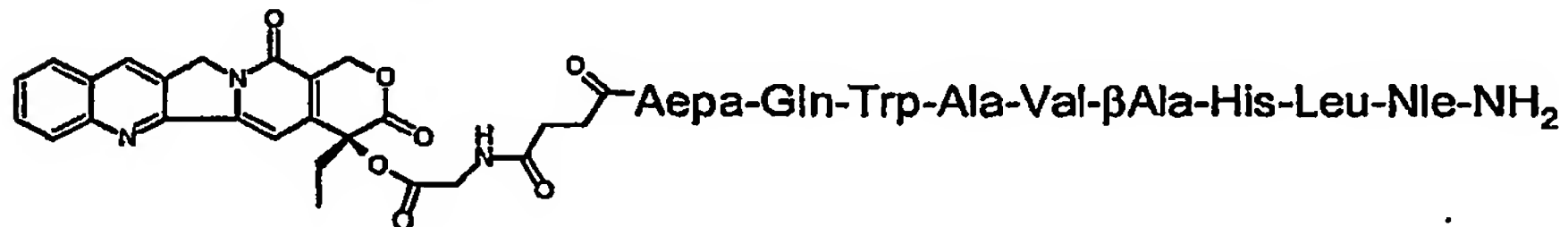
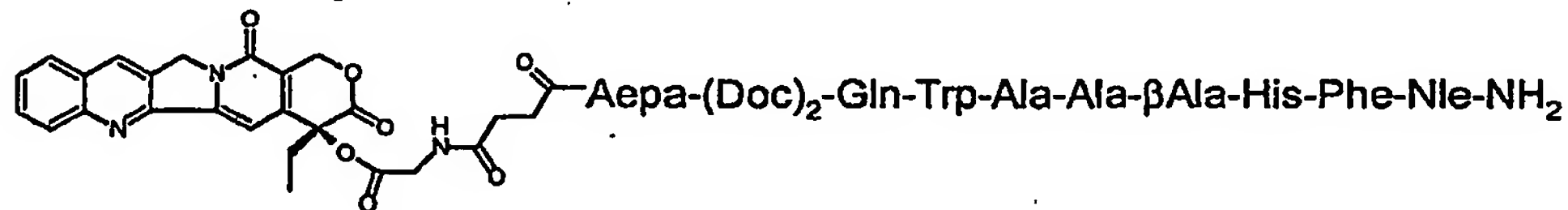
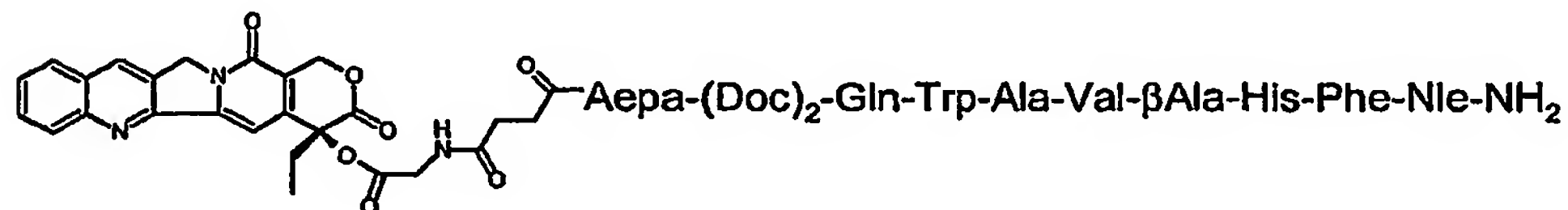
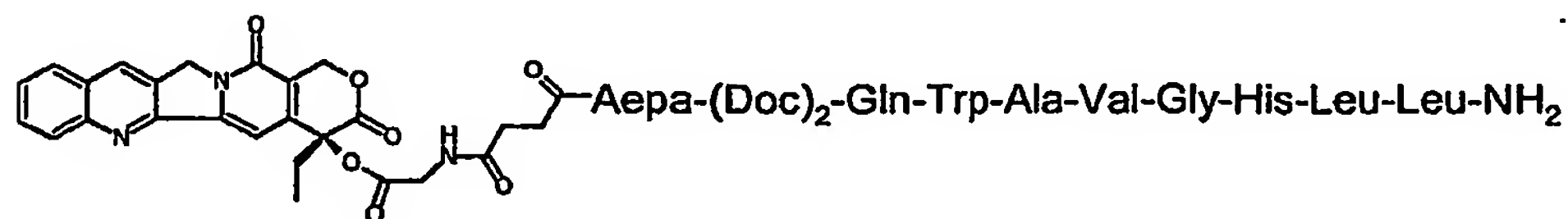
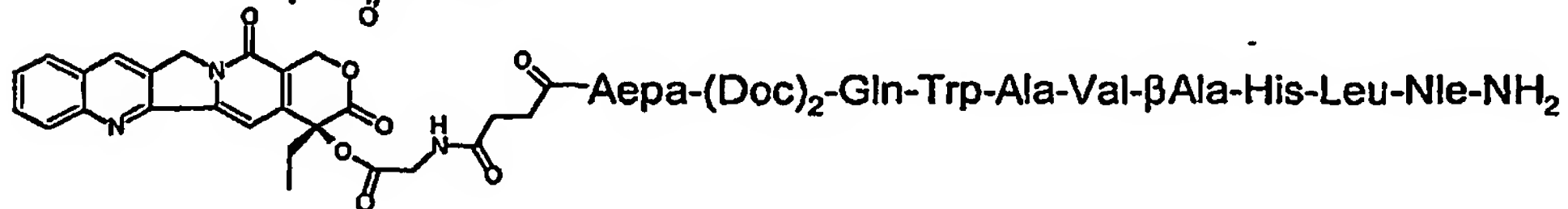
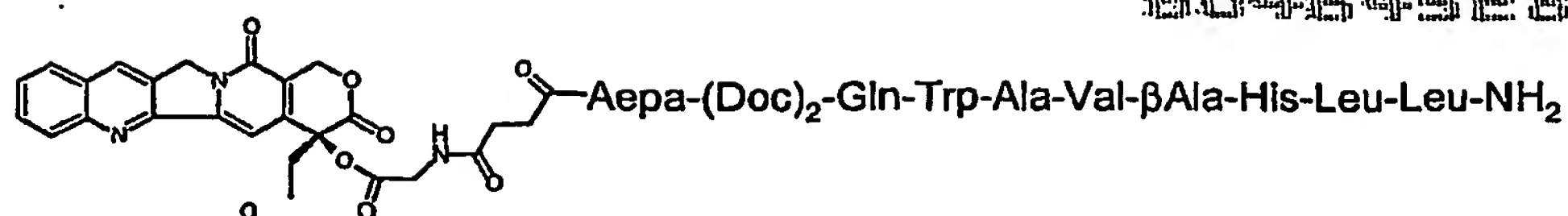


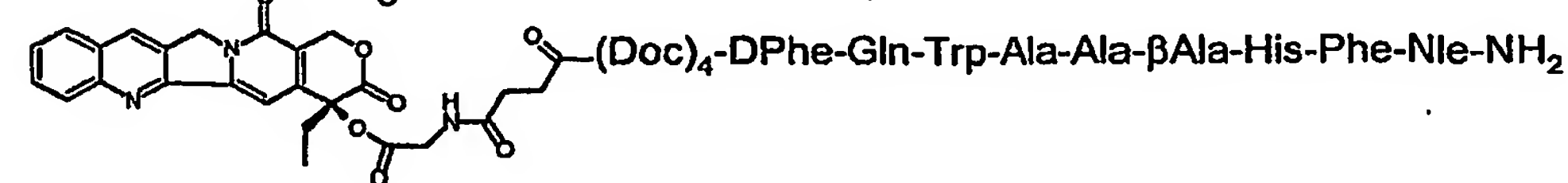
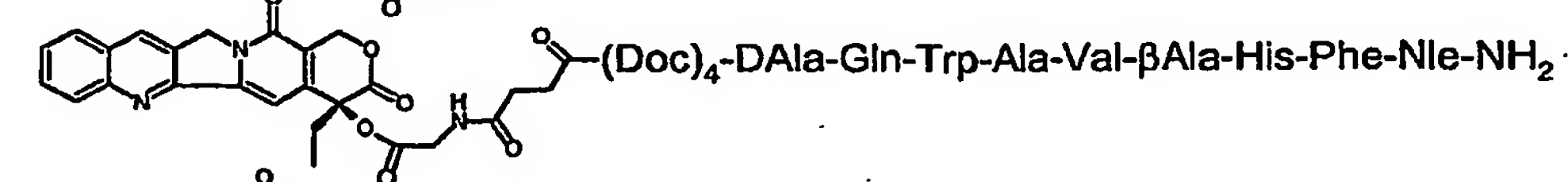
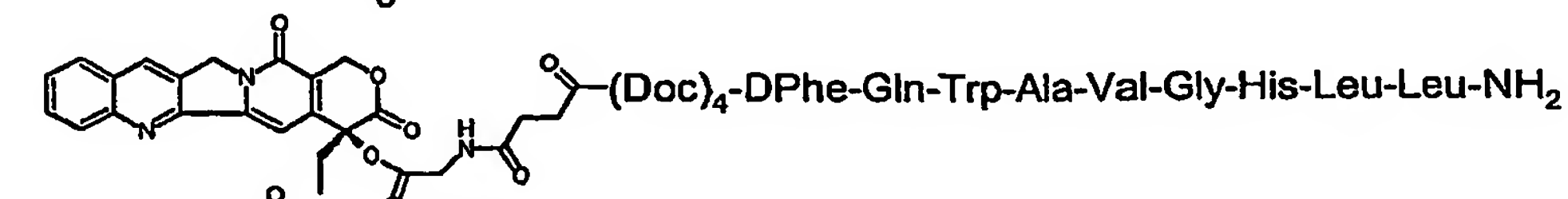
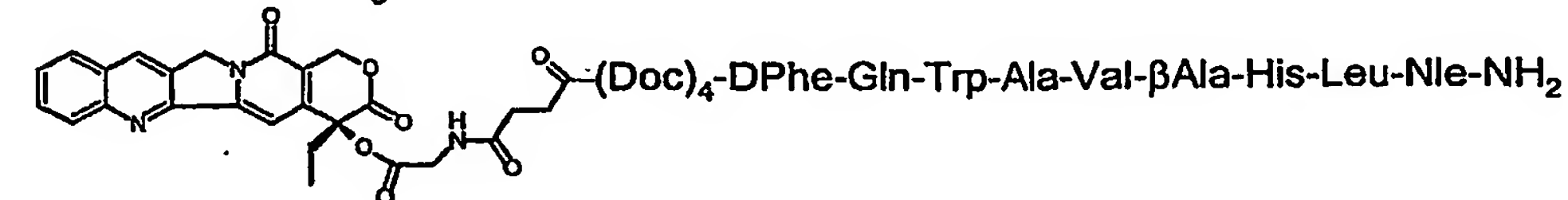
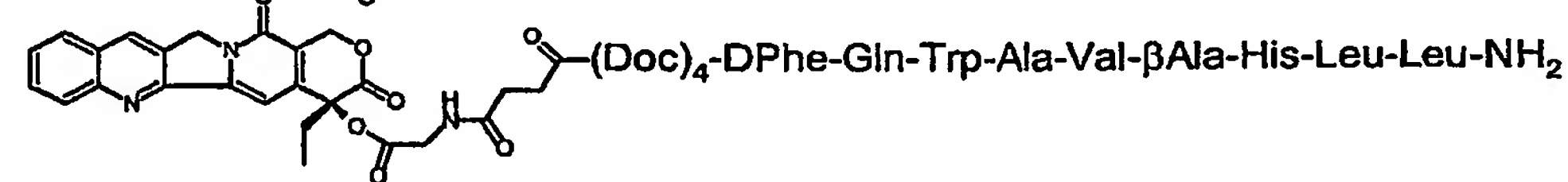
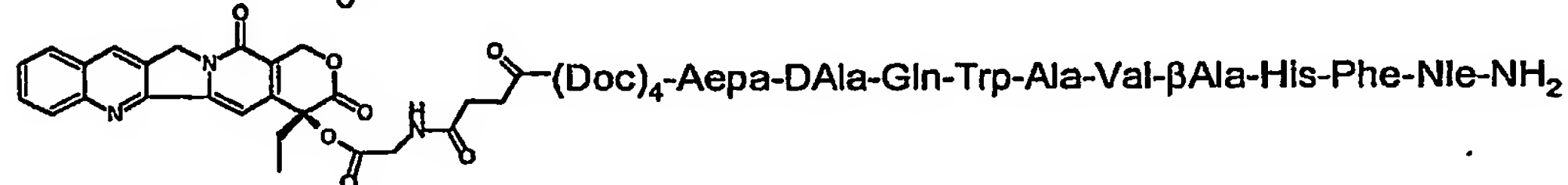
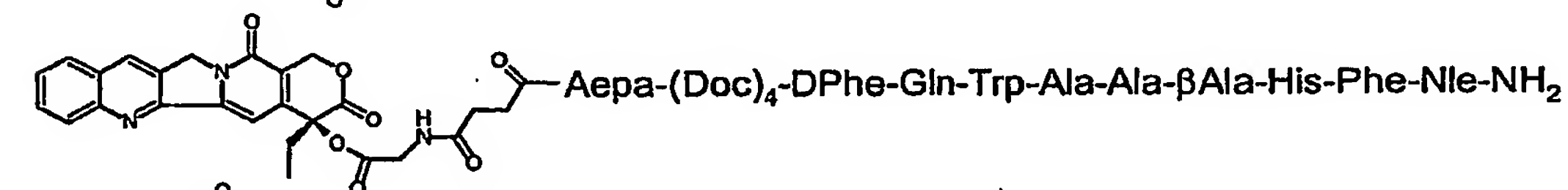
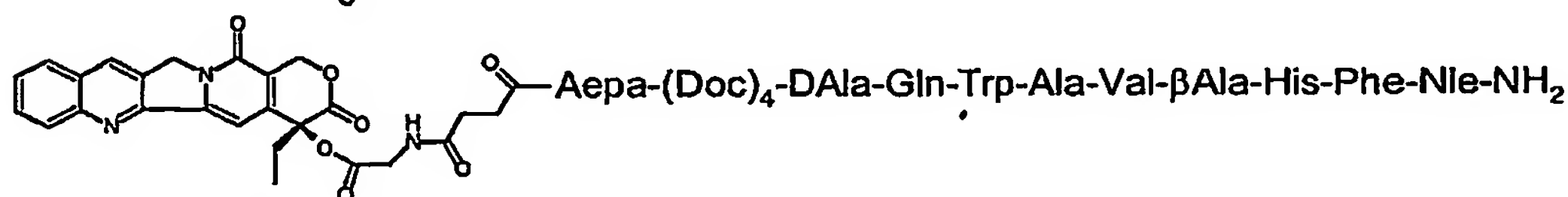
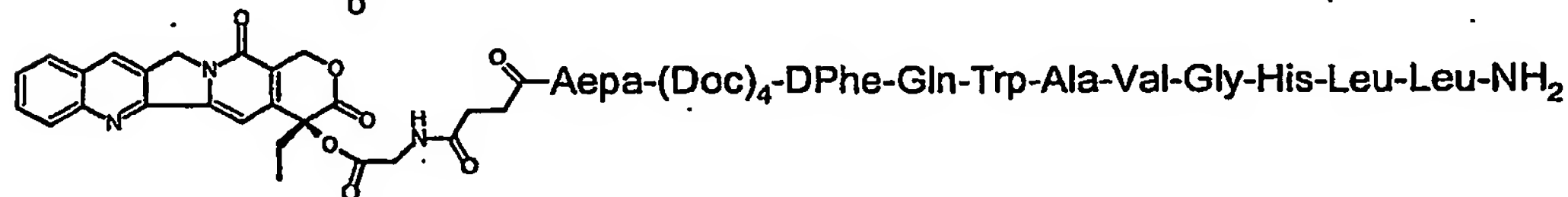
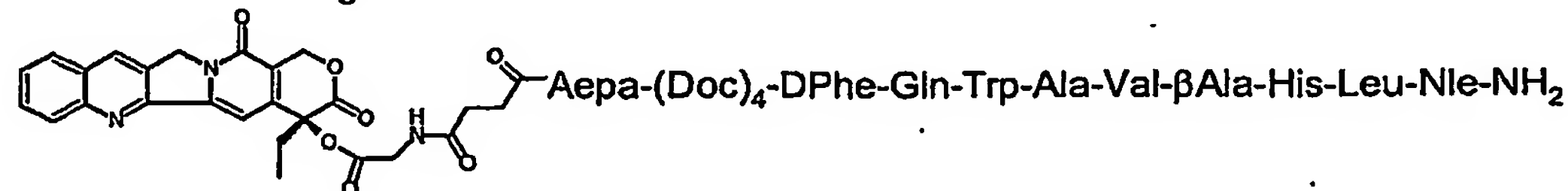
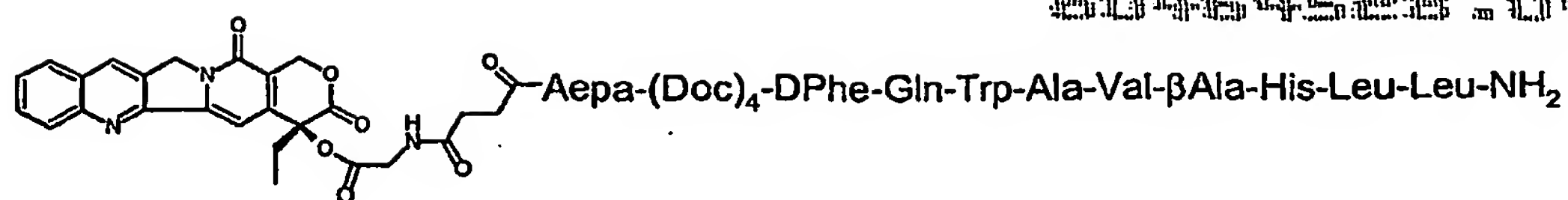


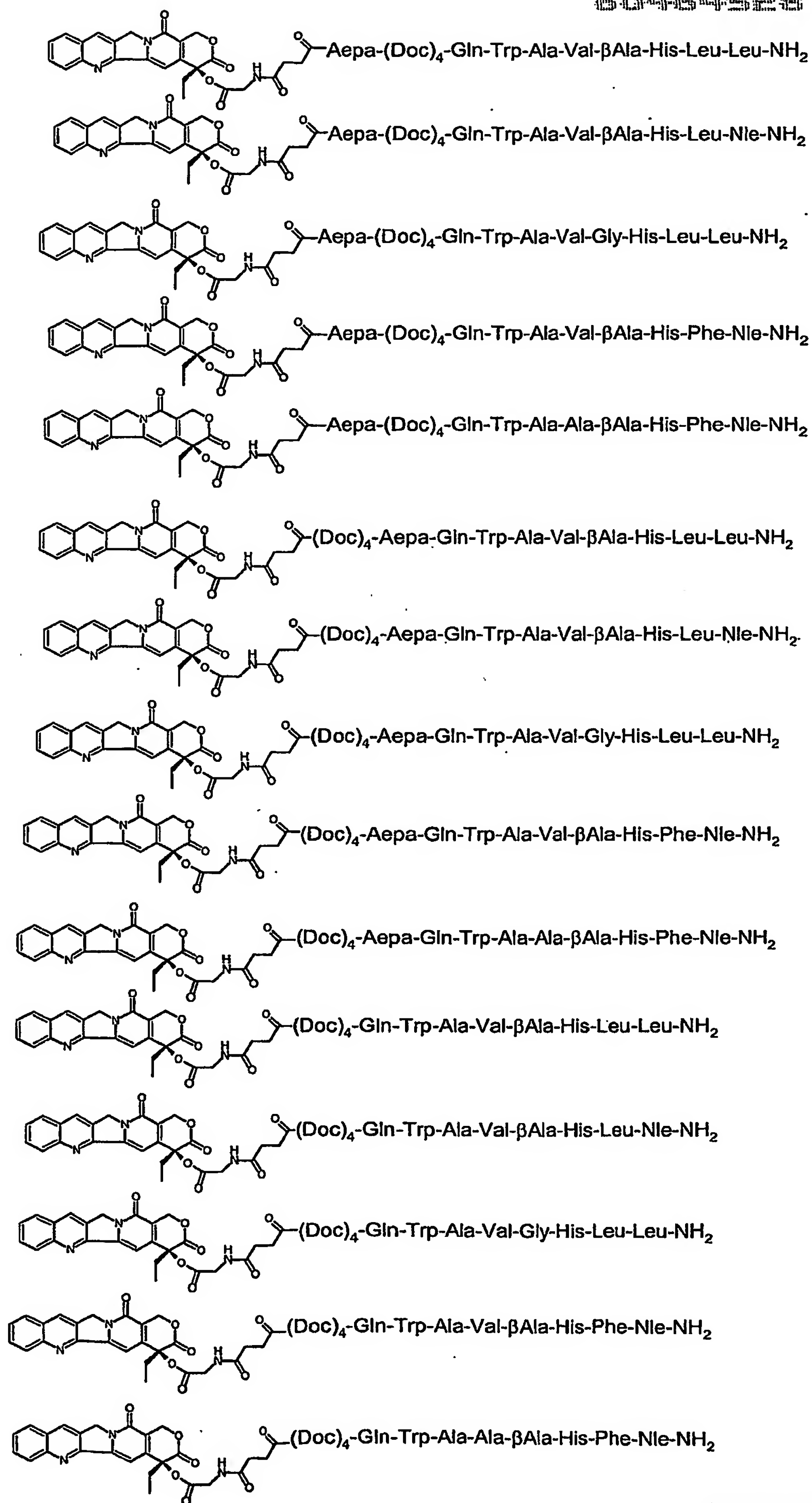


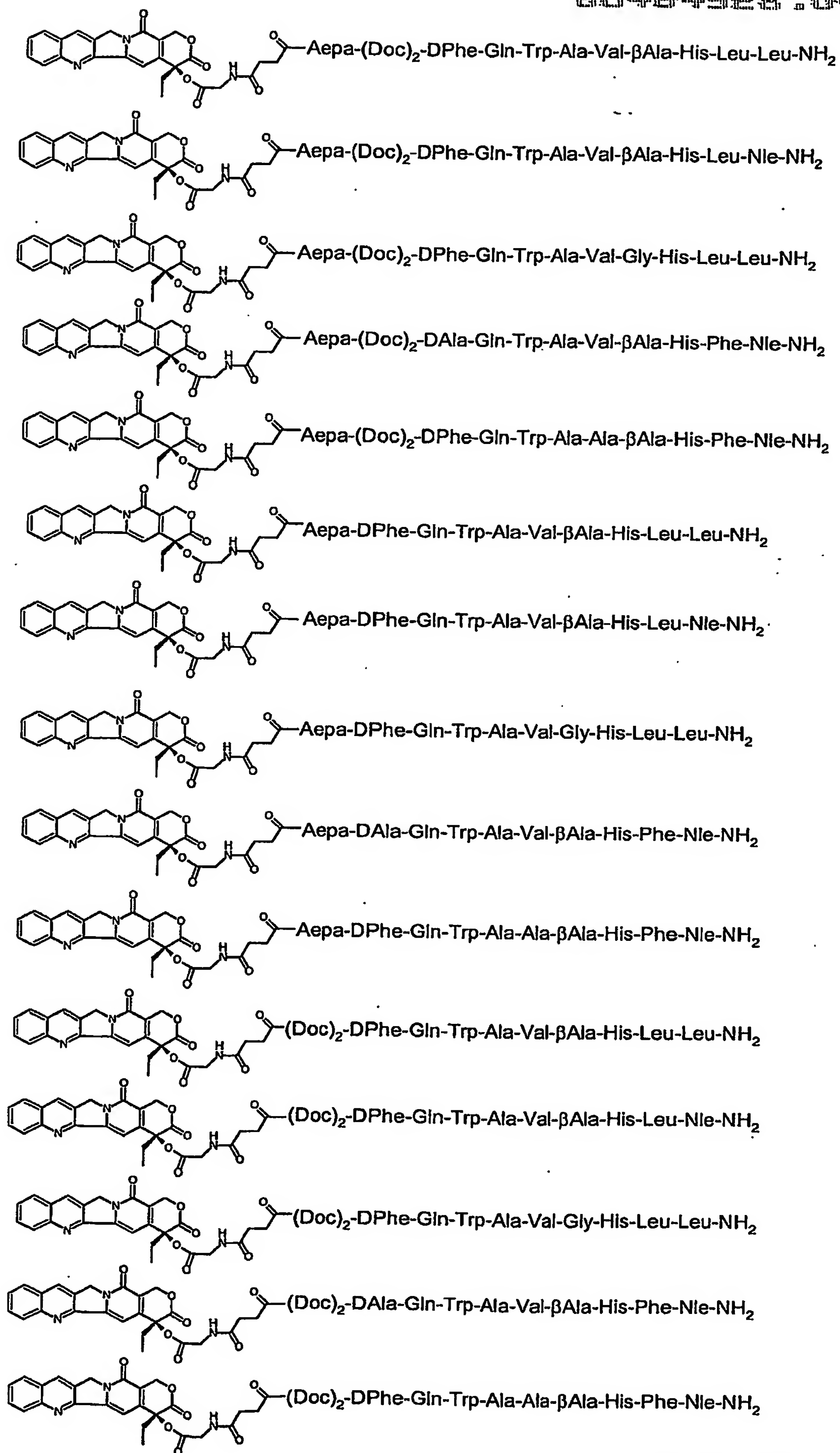
Appendix D

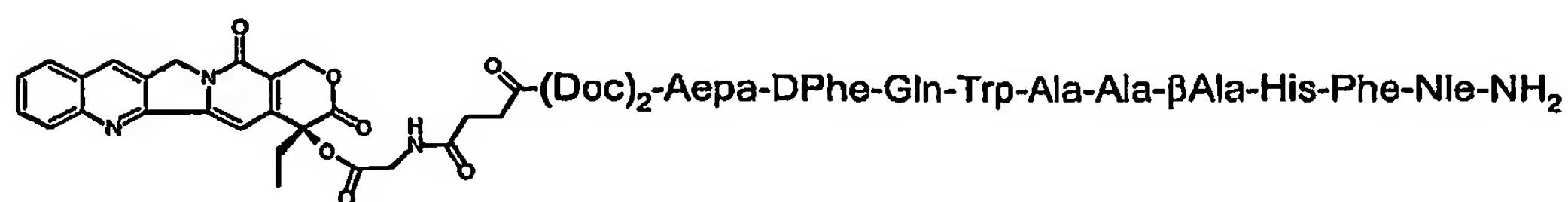
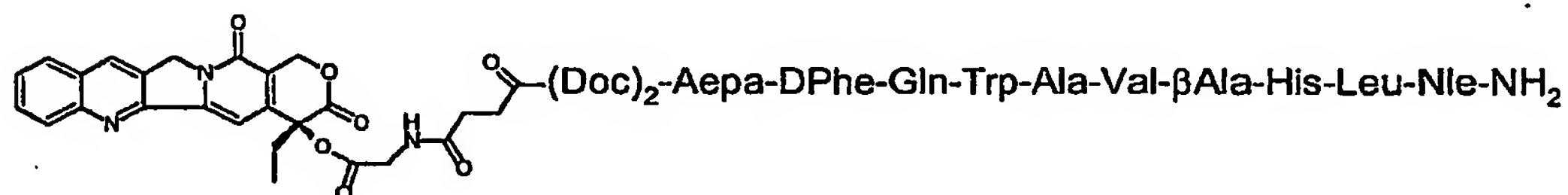
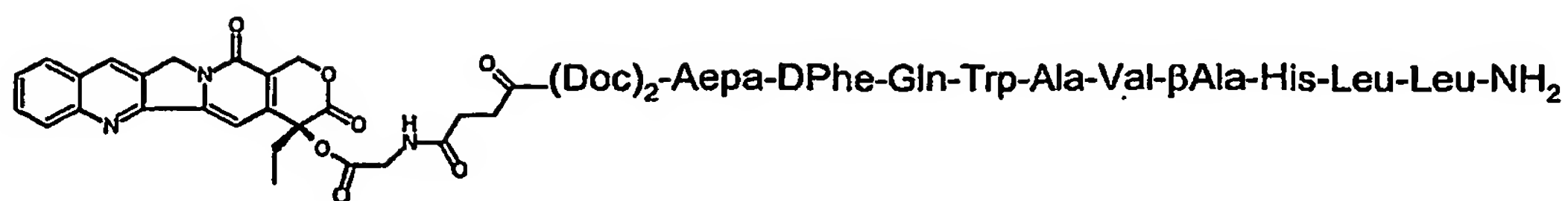


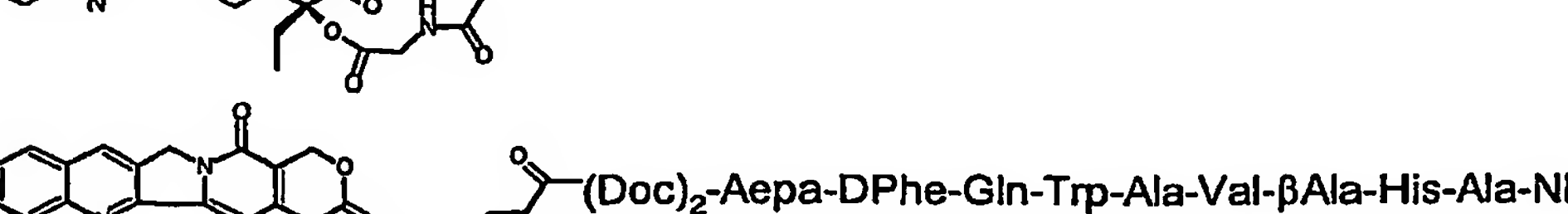
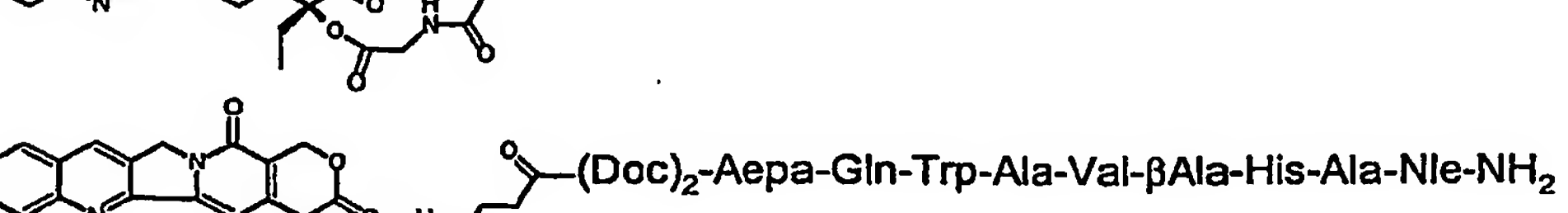
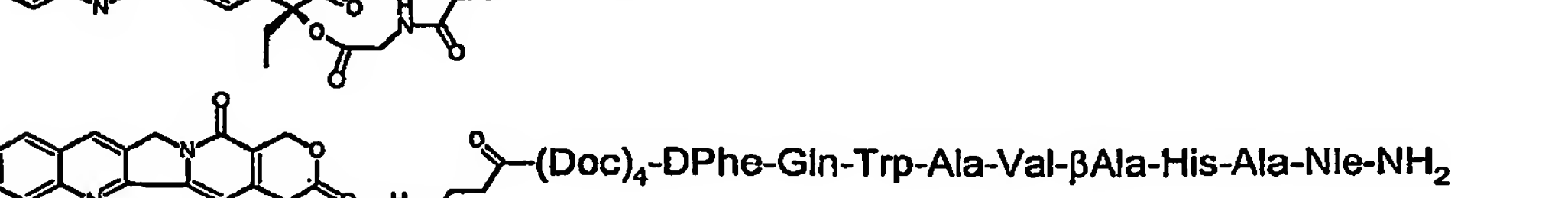
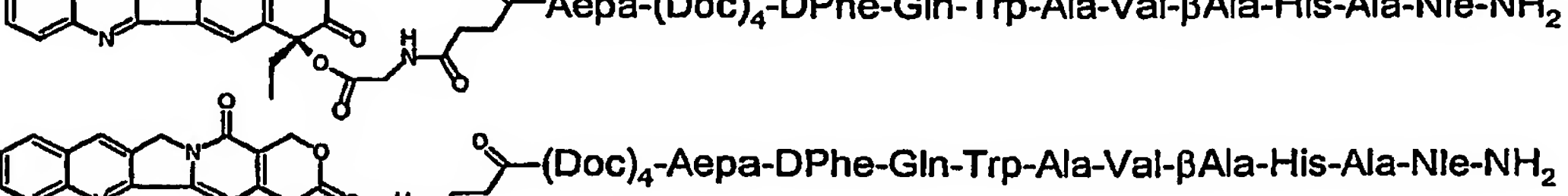
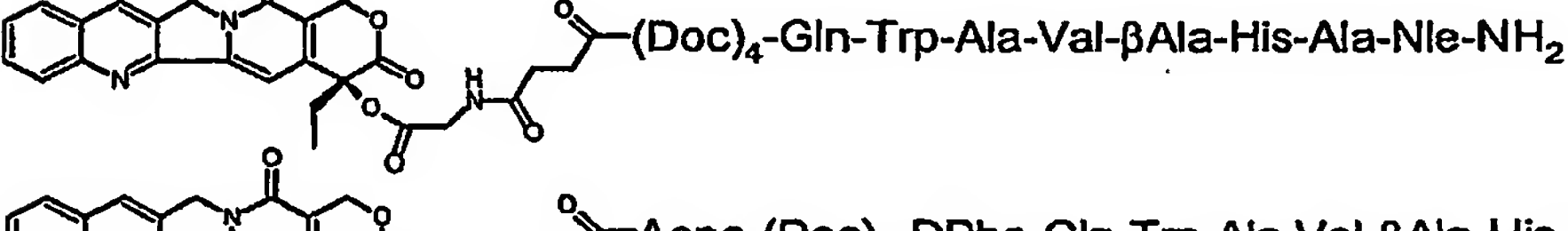
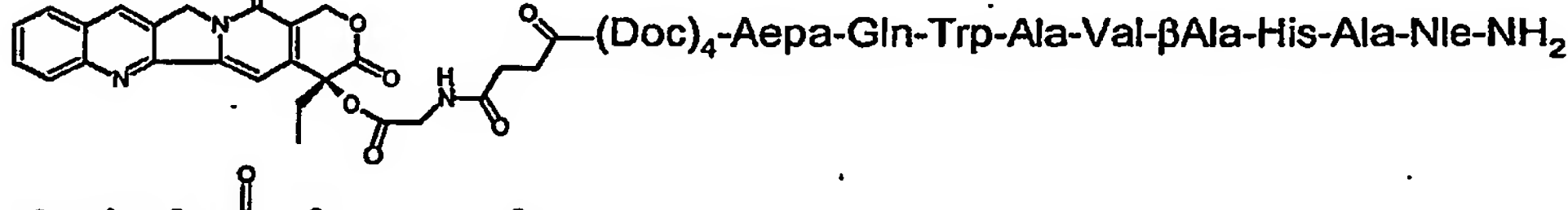
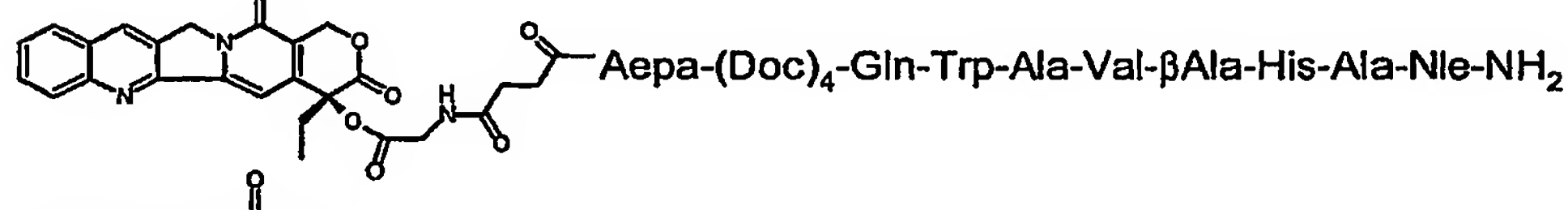
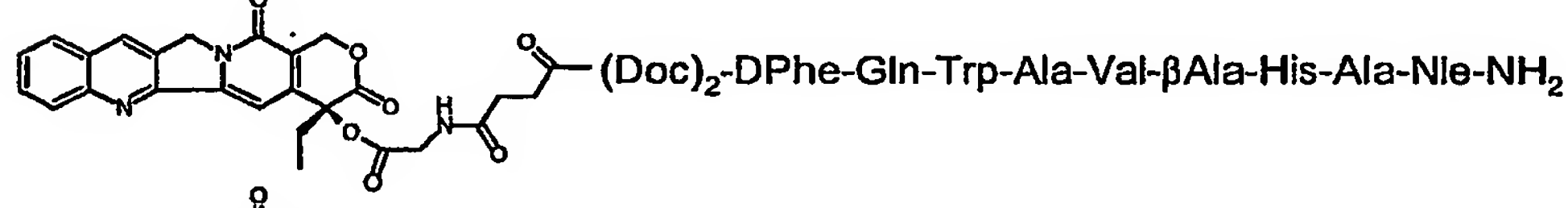
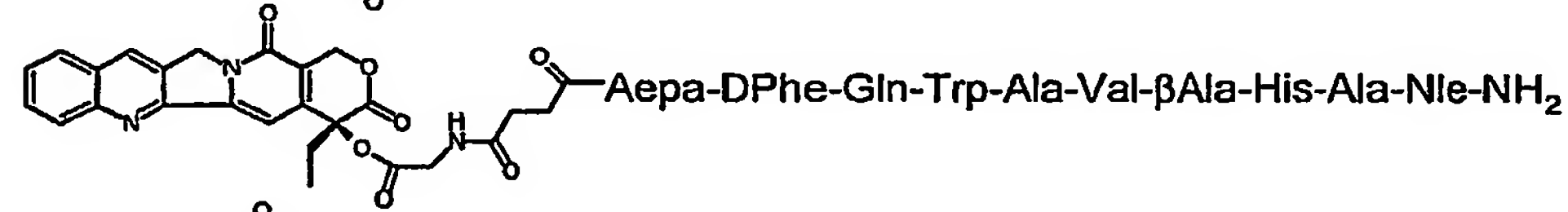
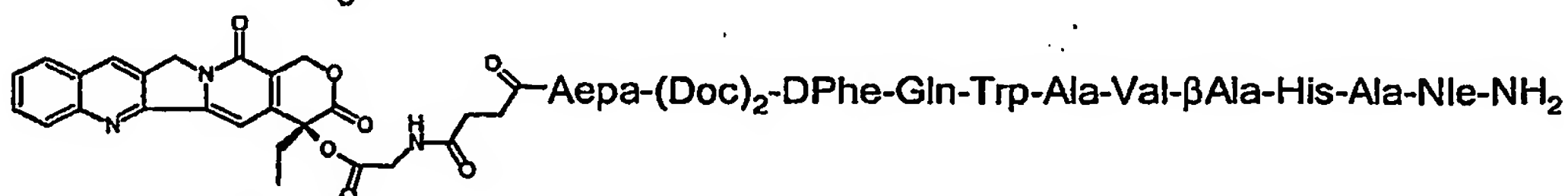
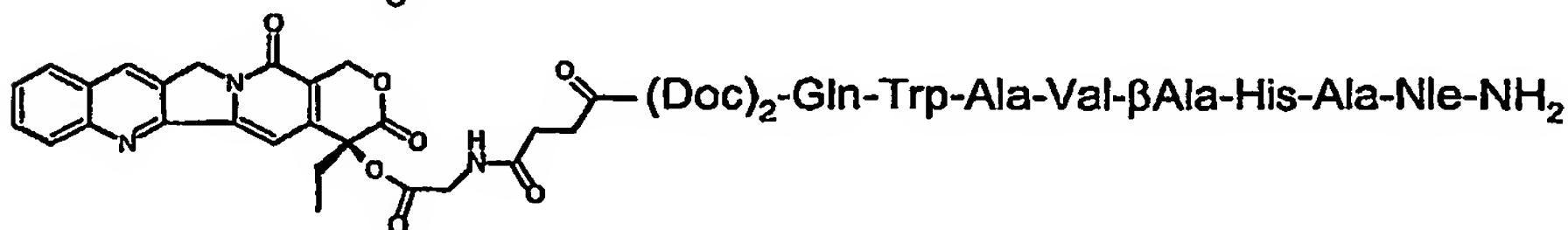
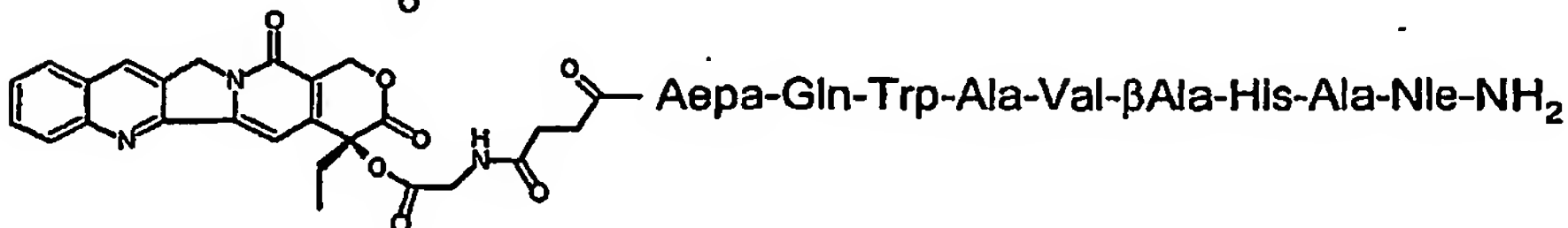
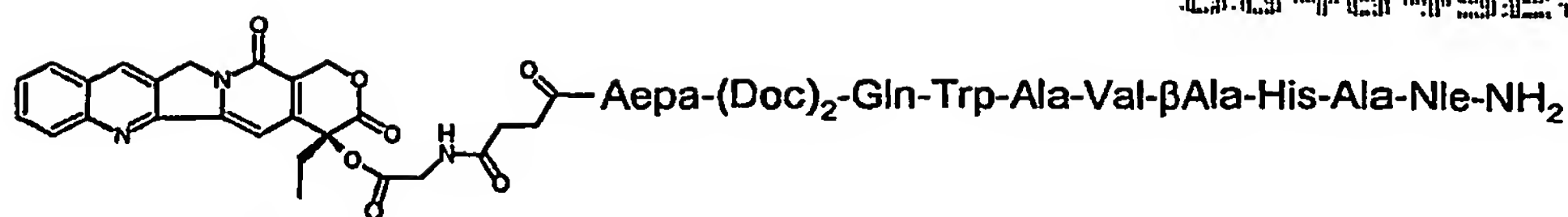


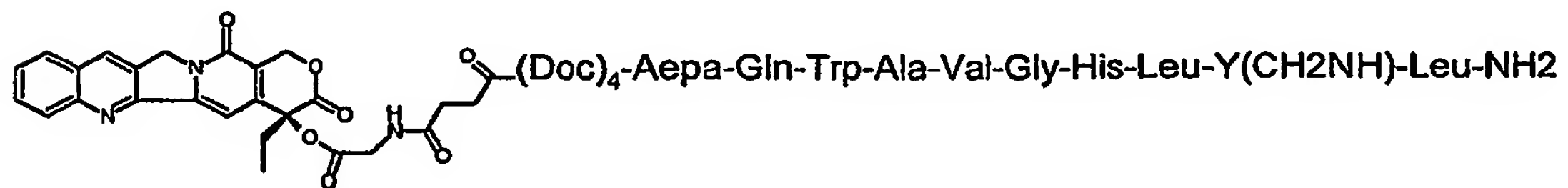
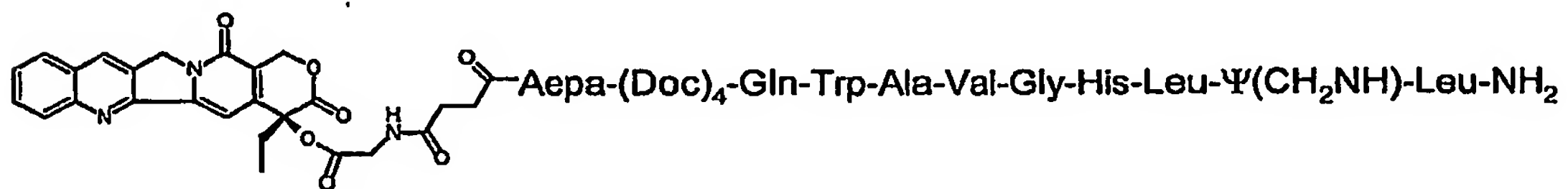
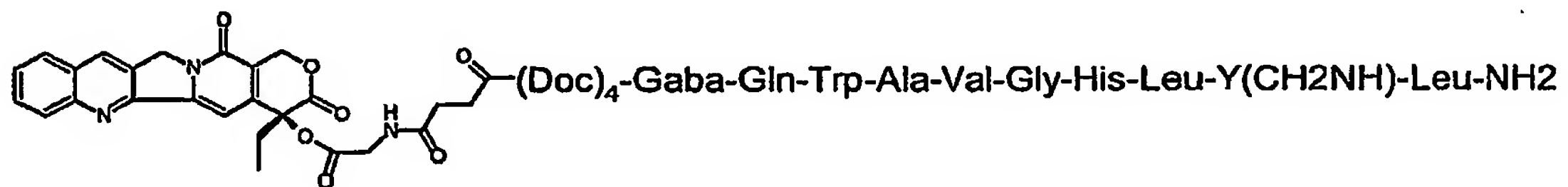
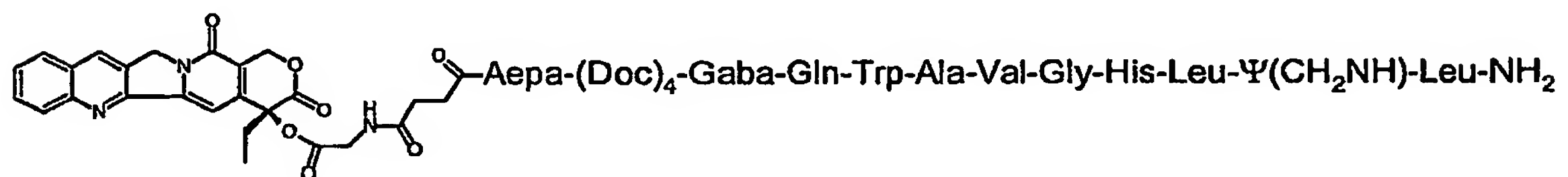
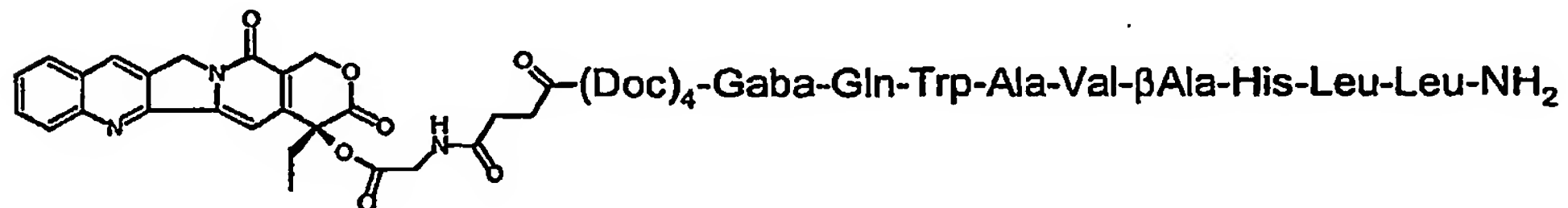
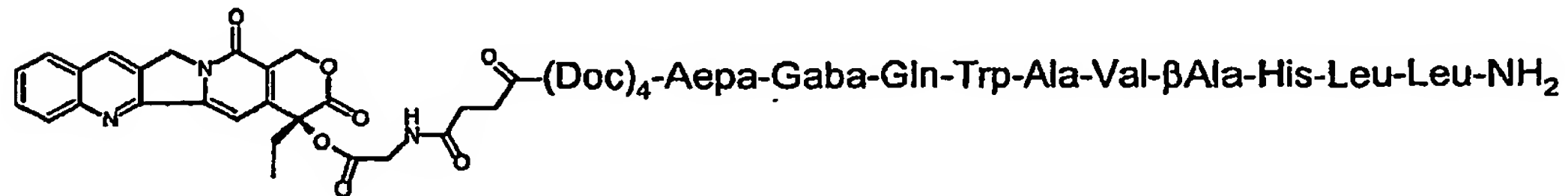
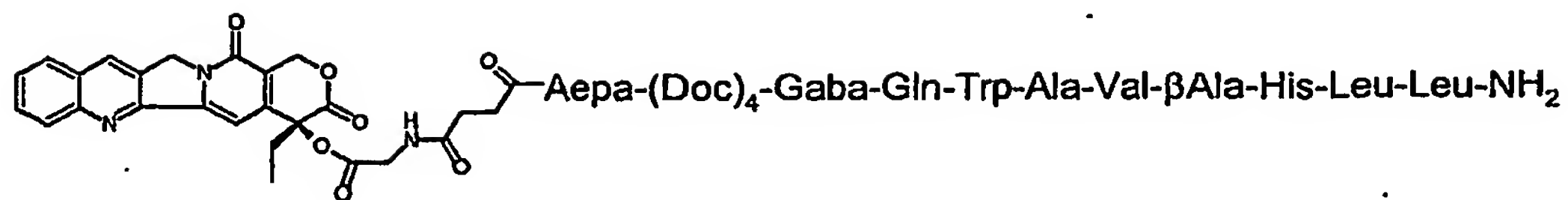


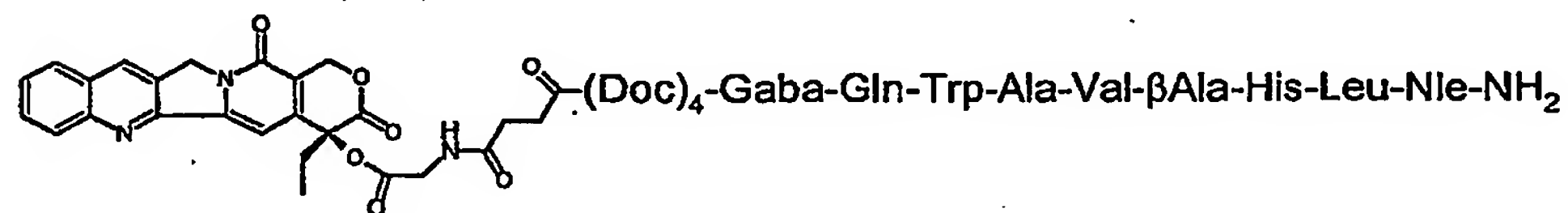
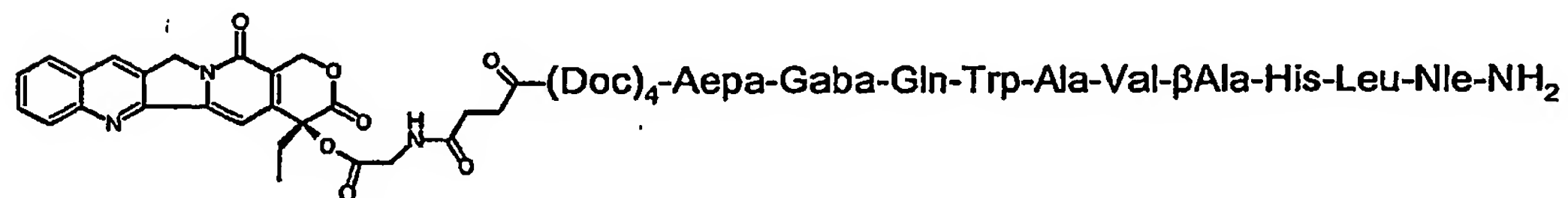
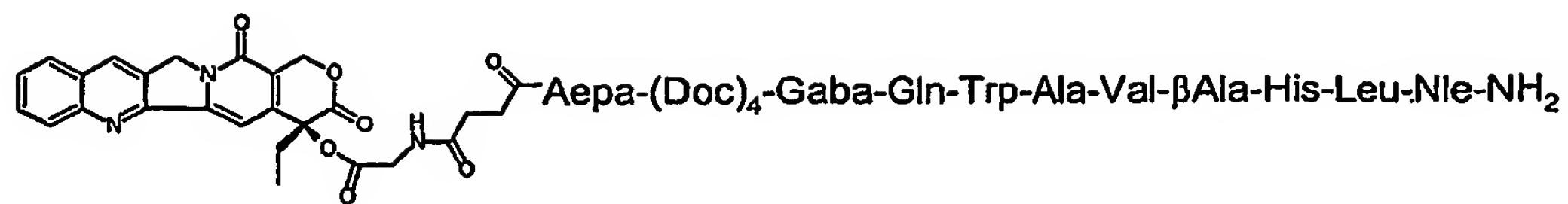


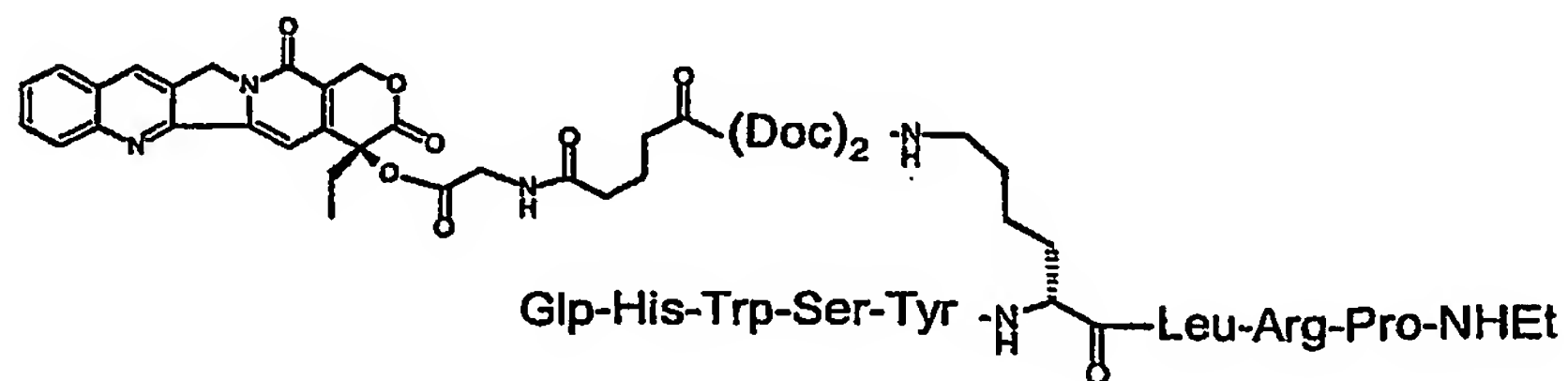
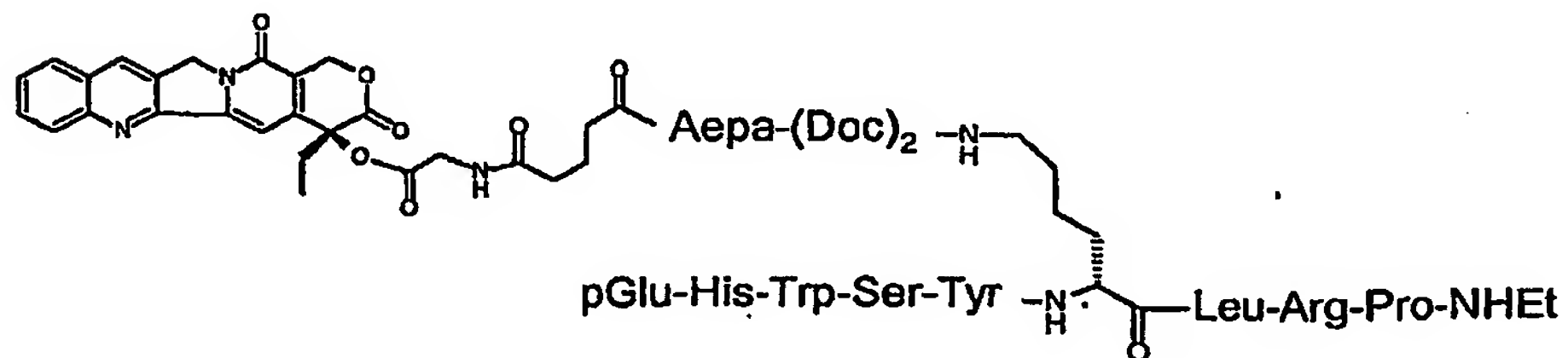
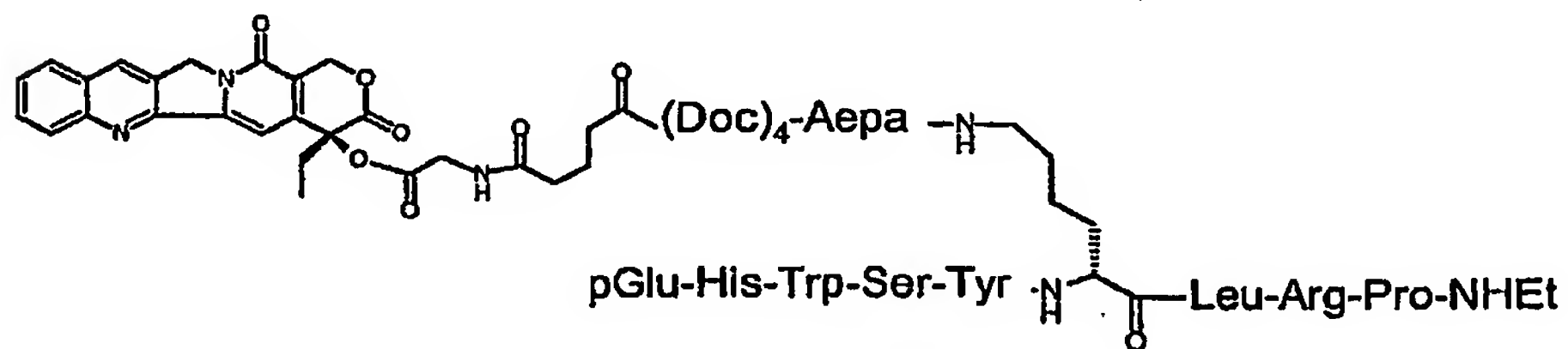
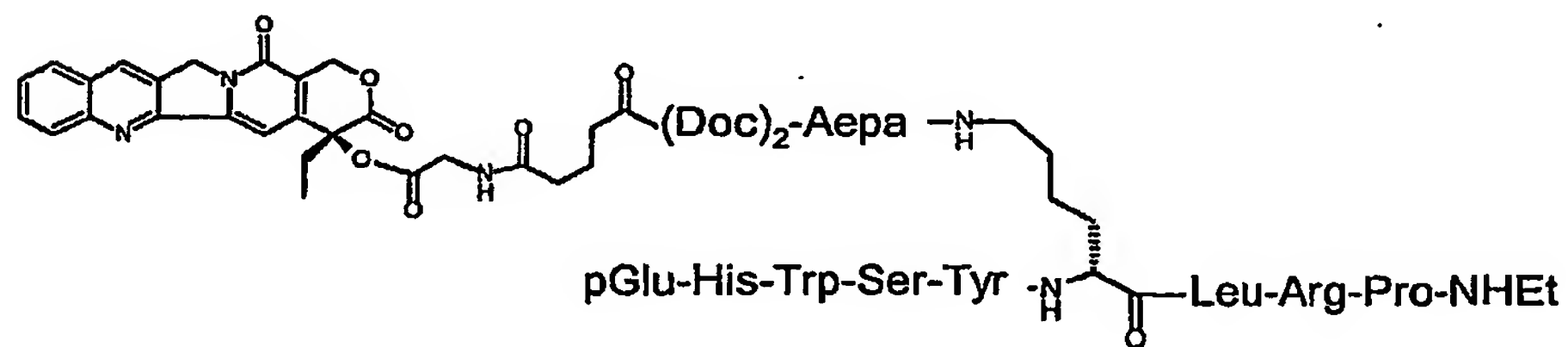
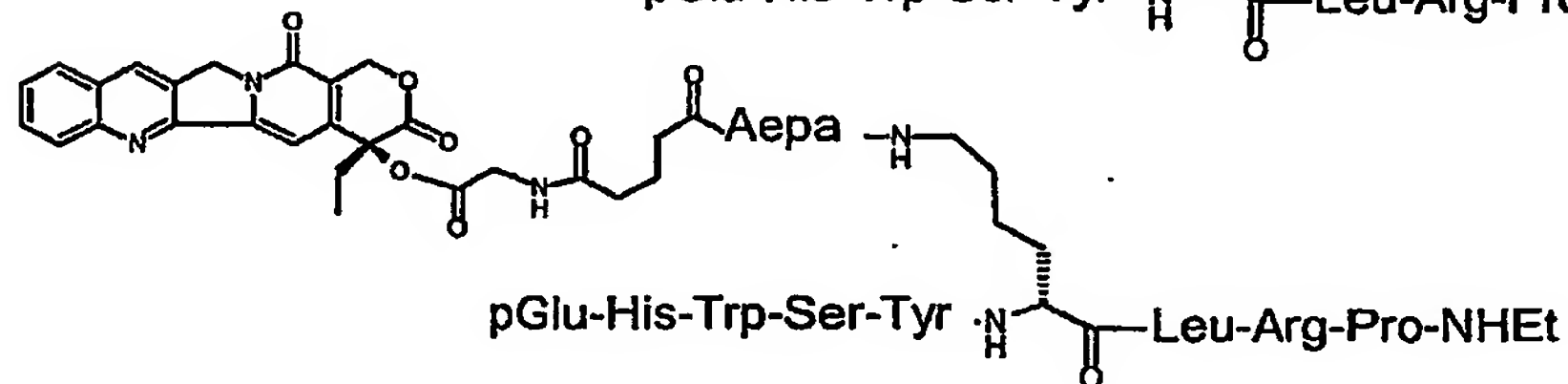
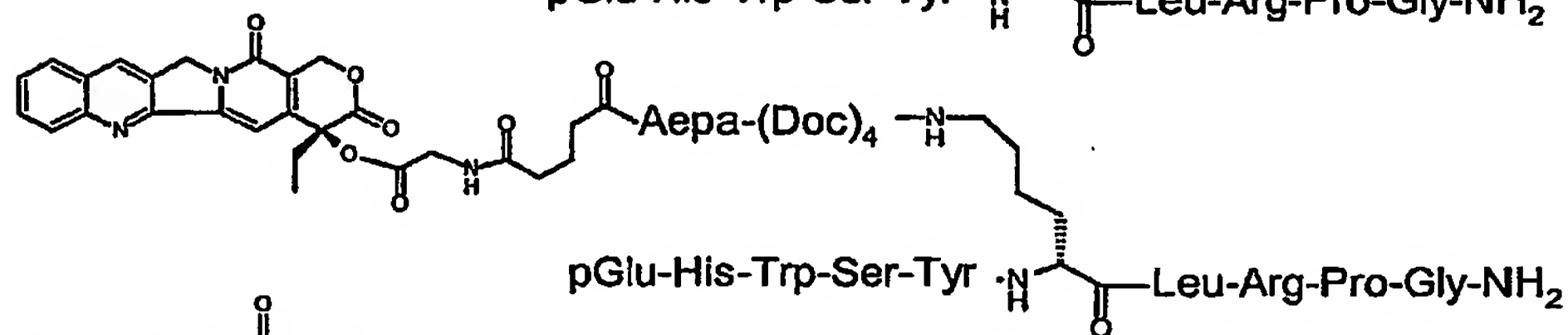
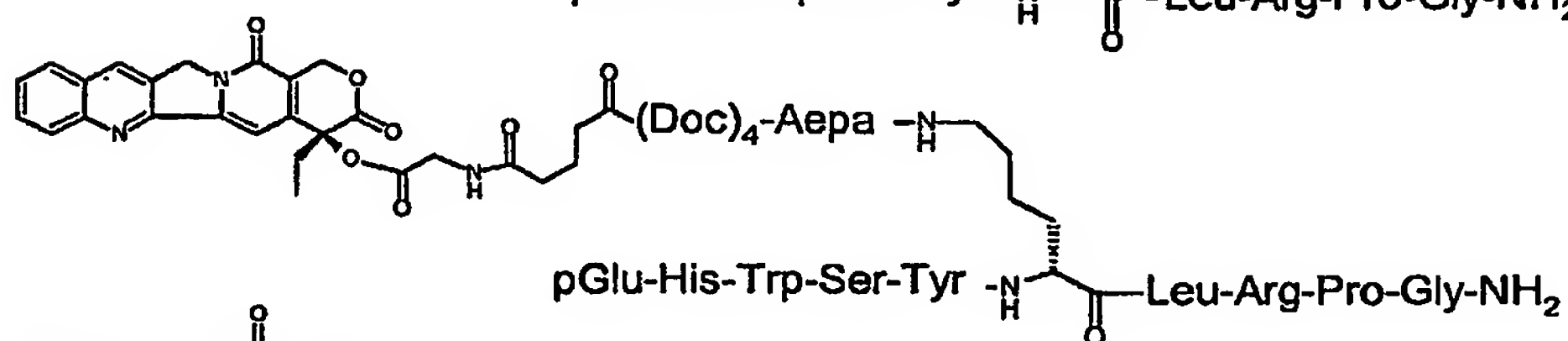
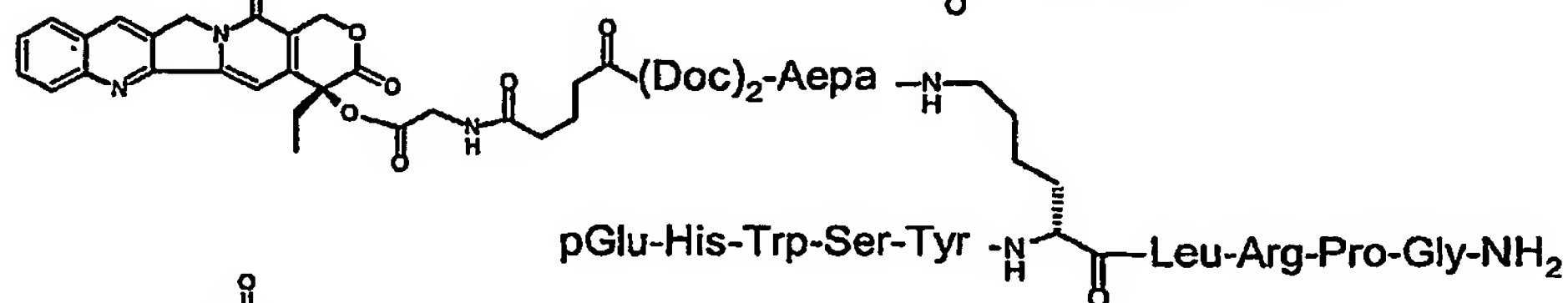
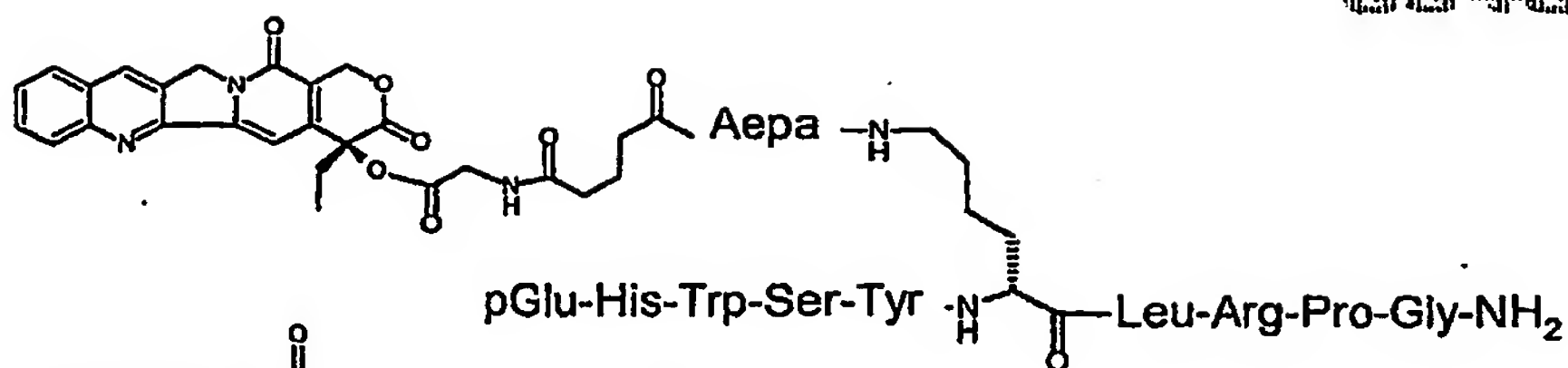




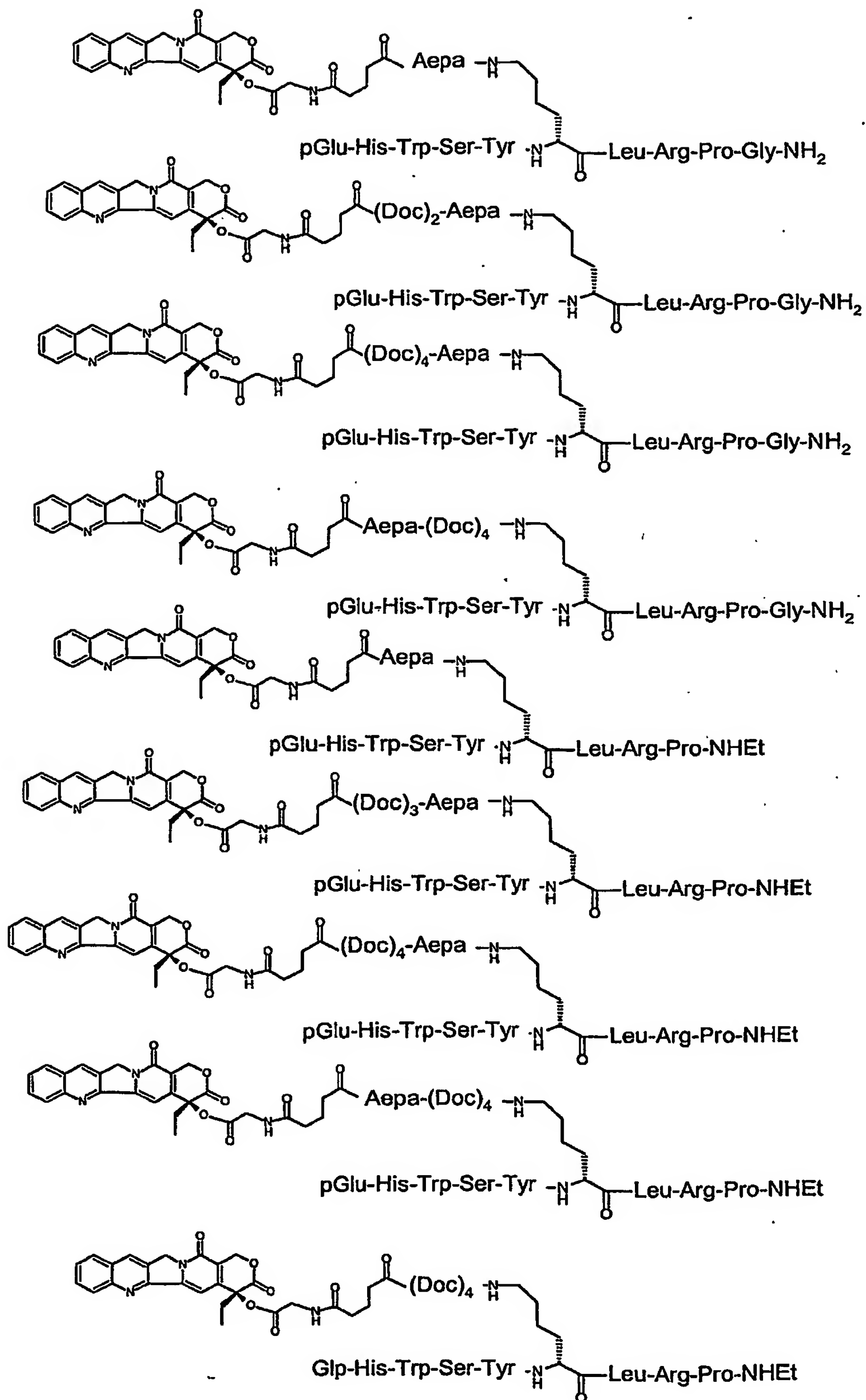


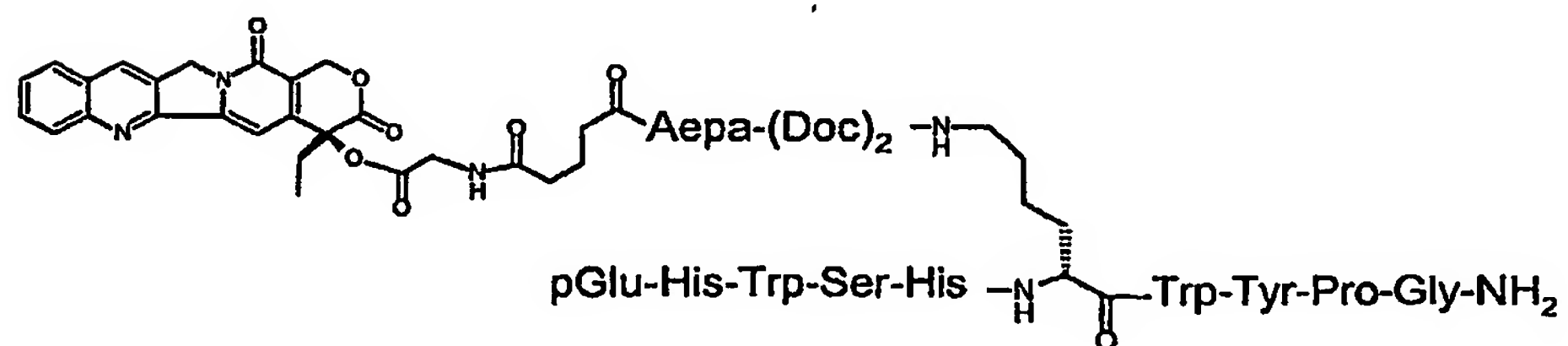
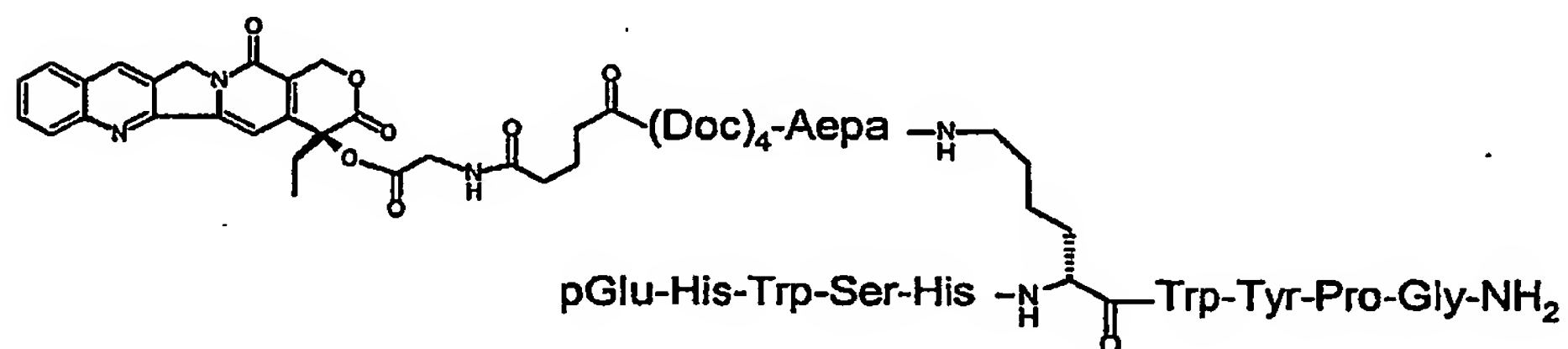
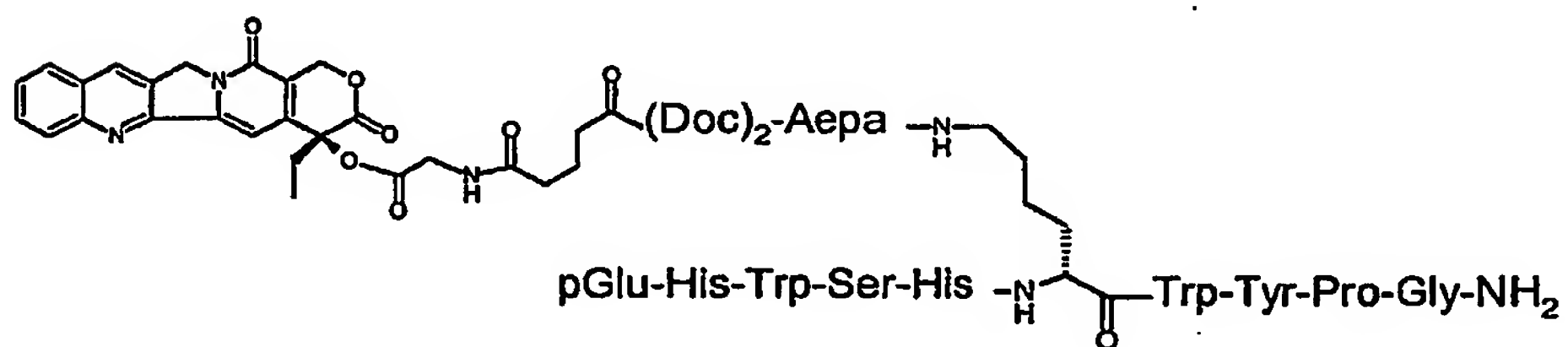
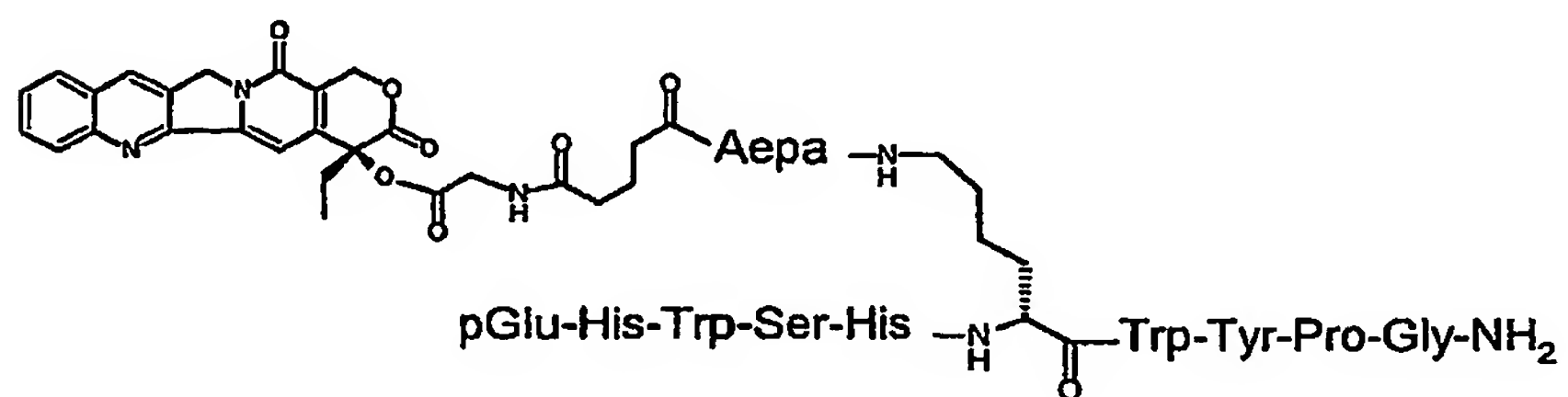
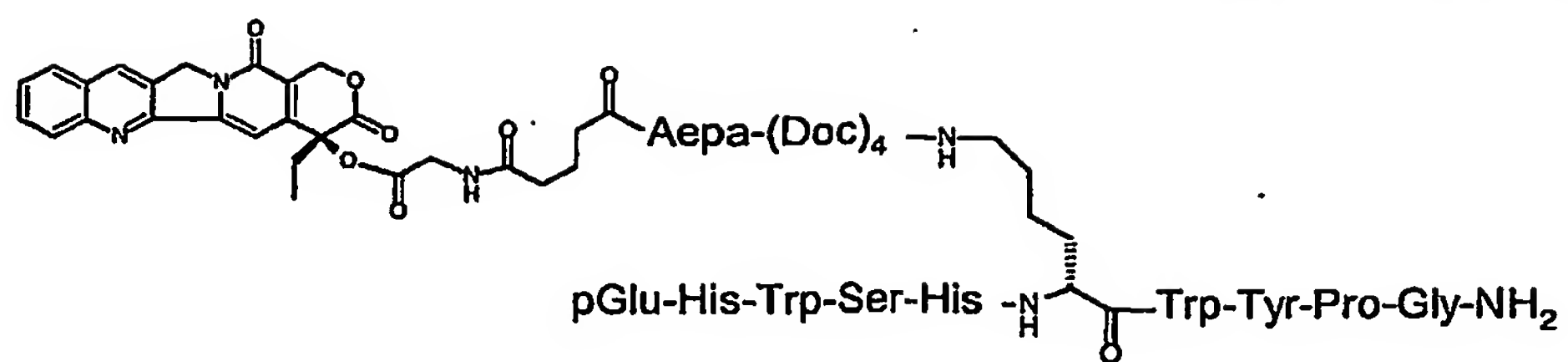


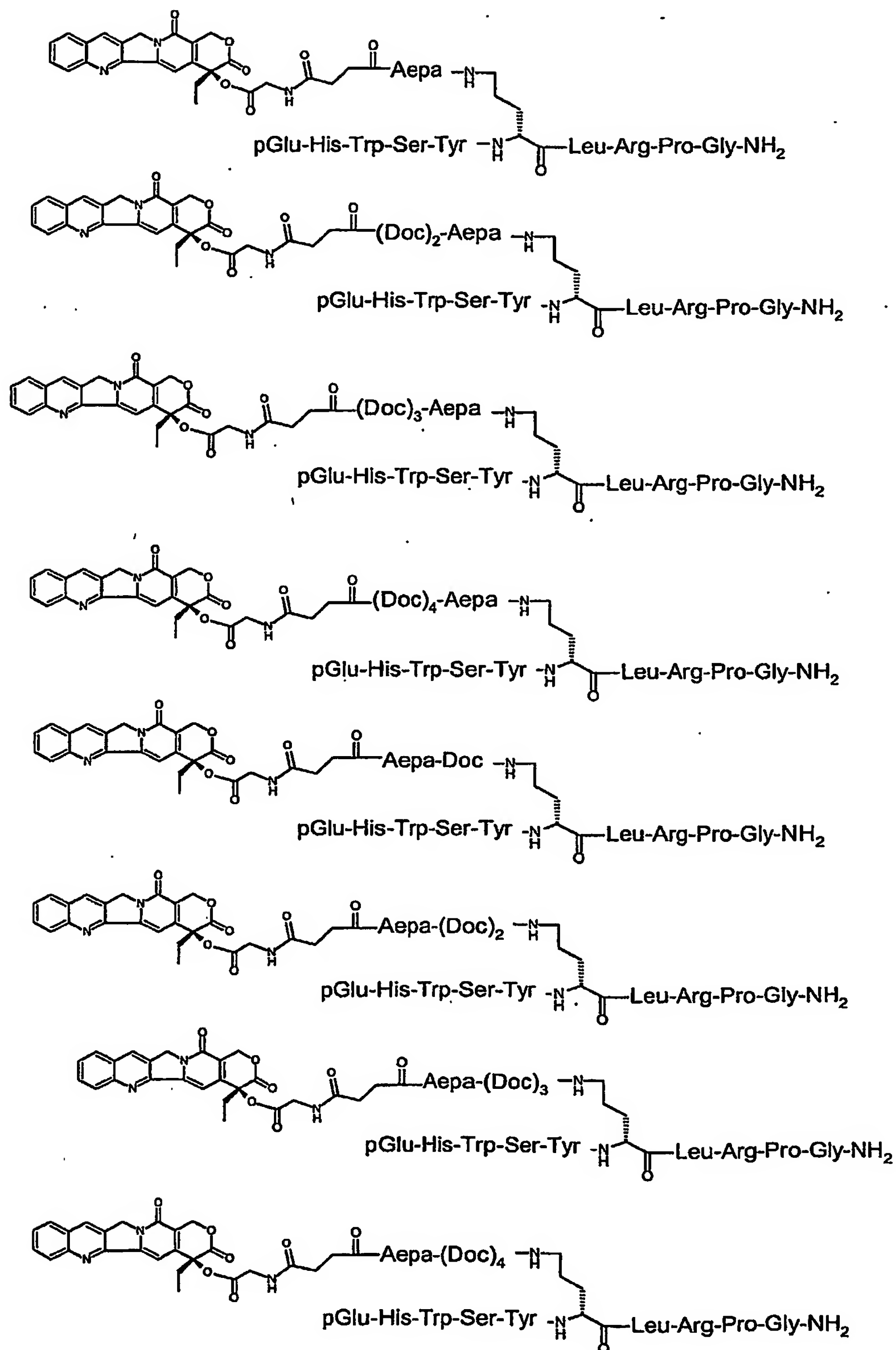


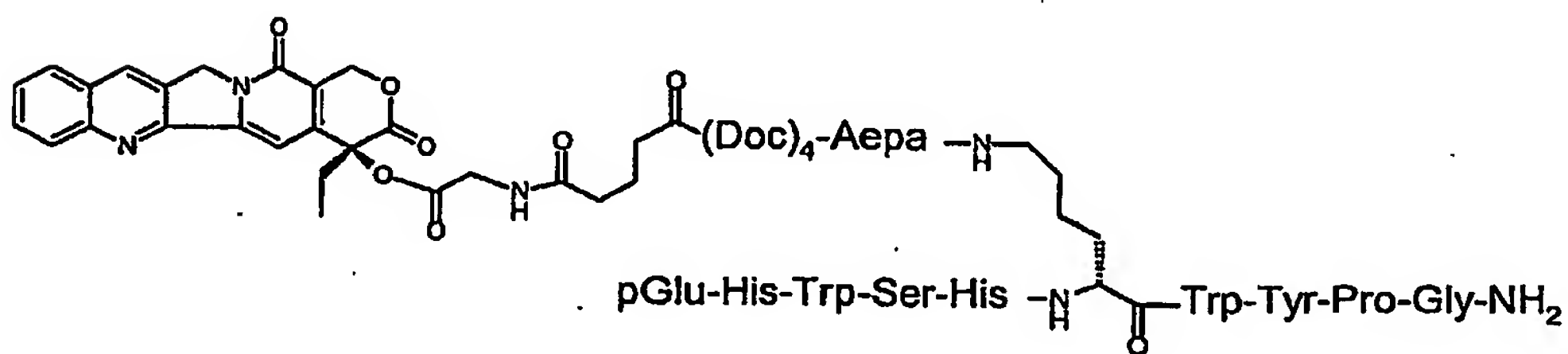
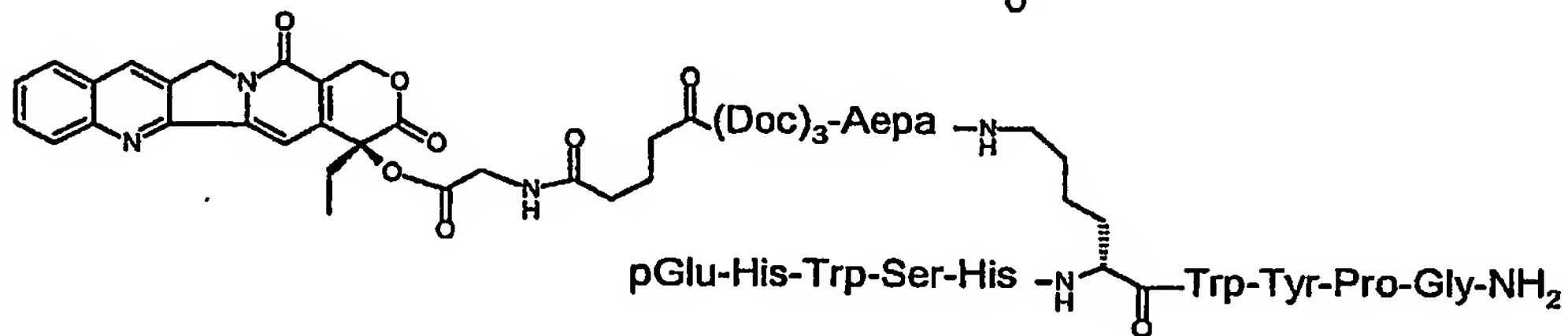
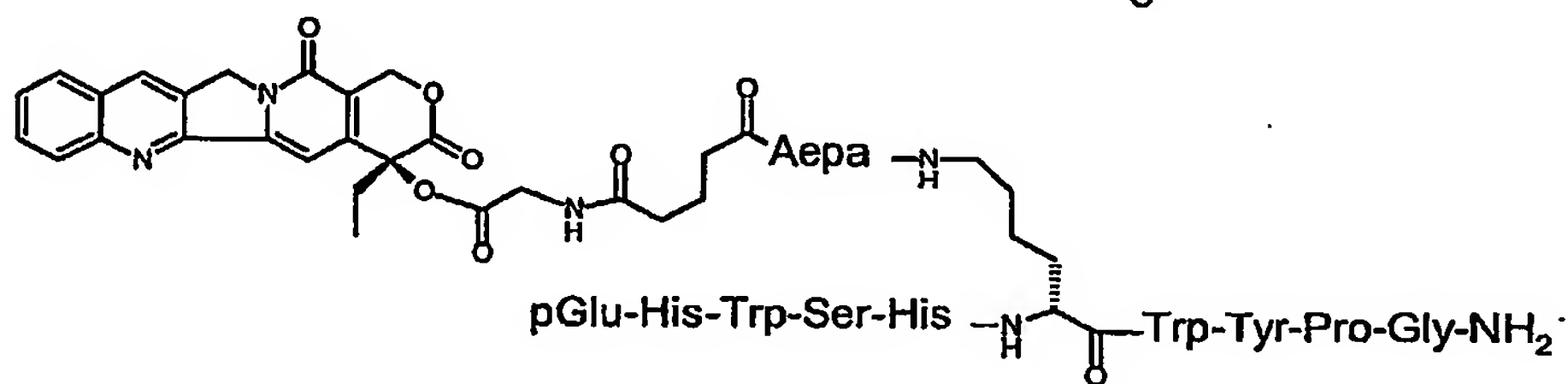
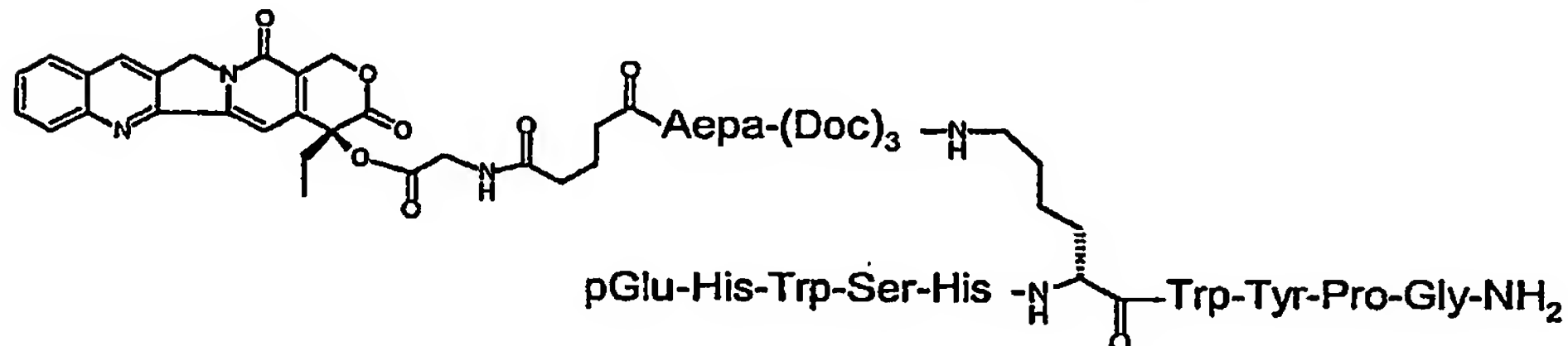
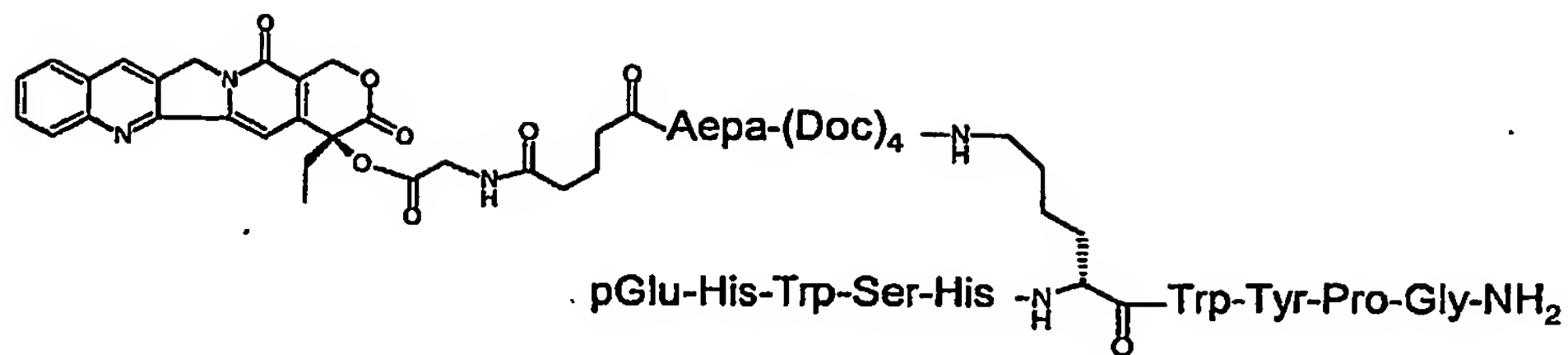


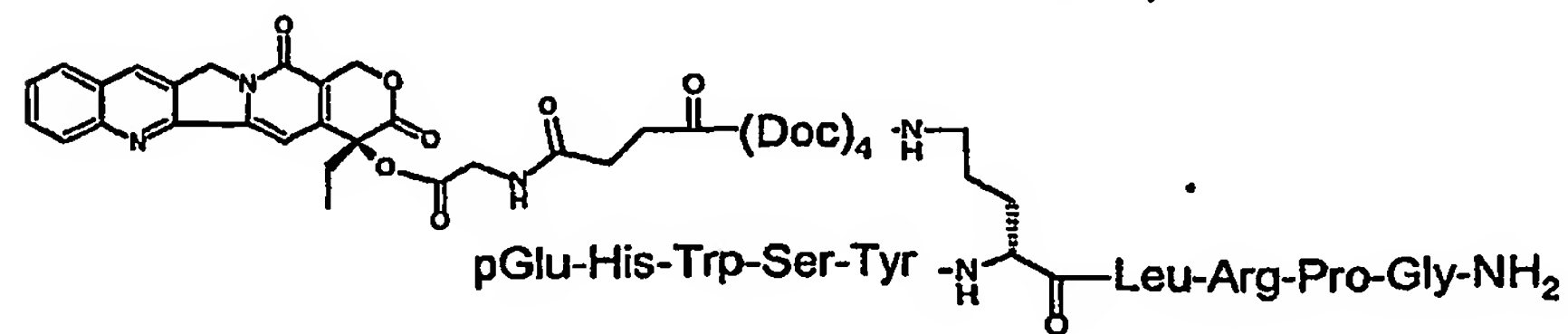
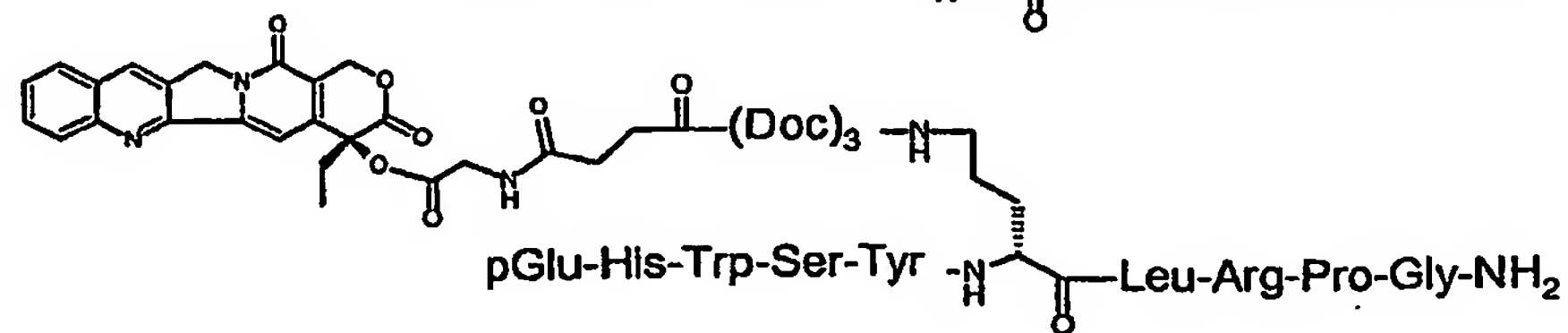
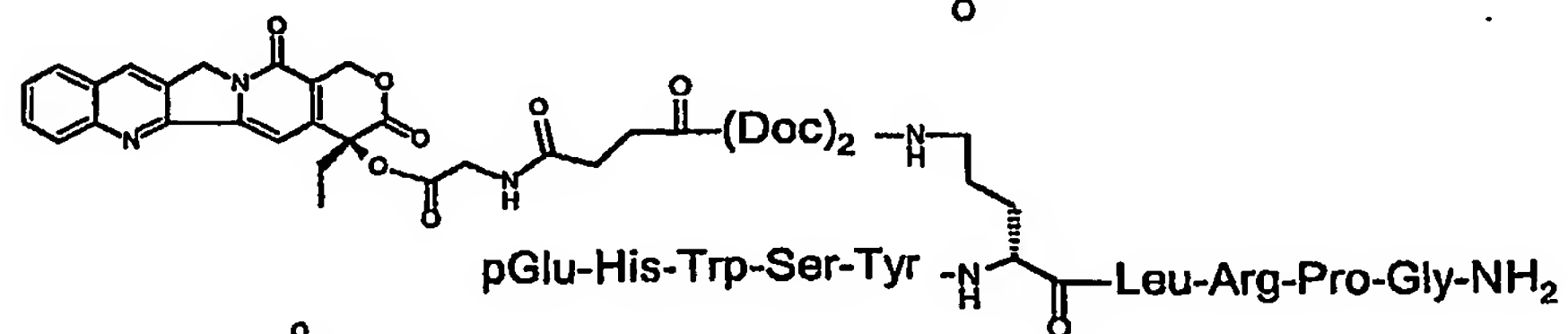
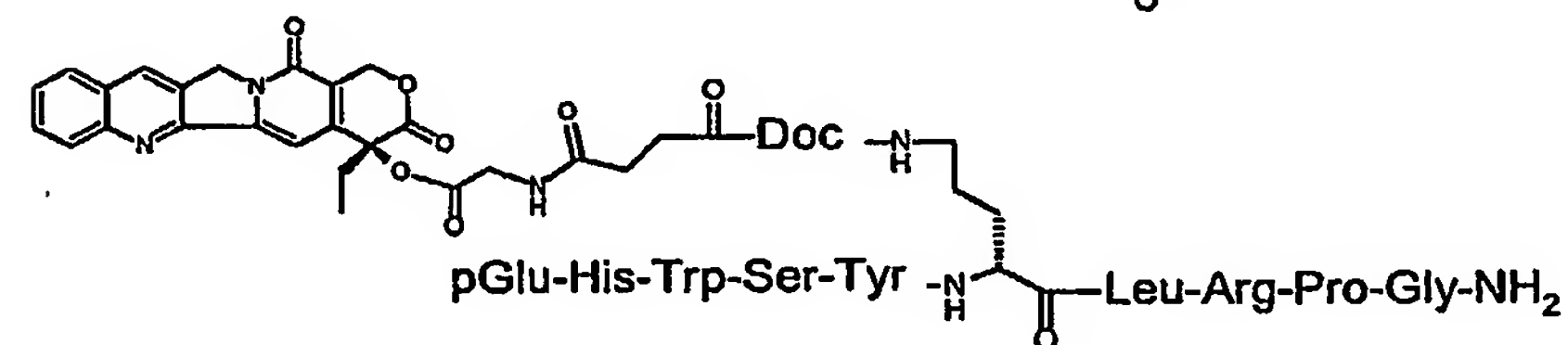
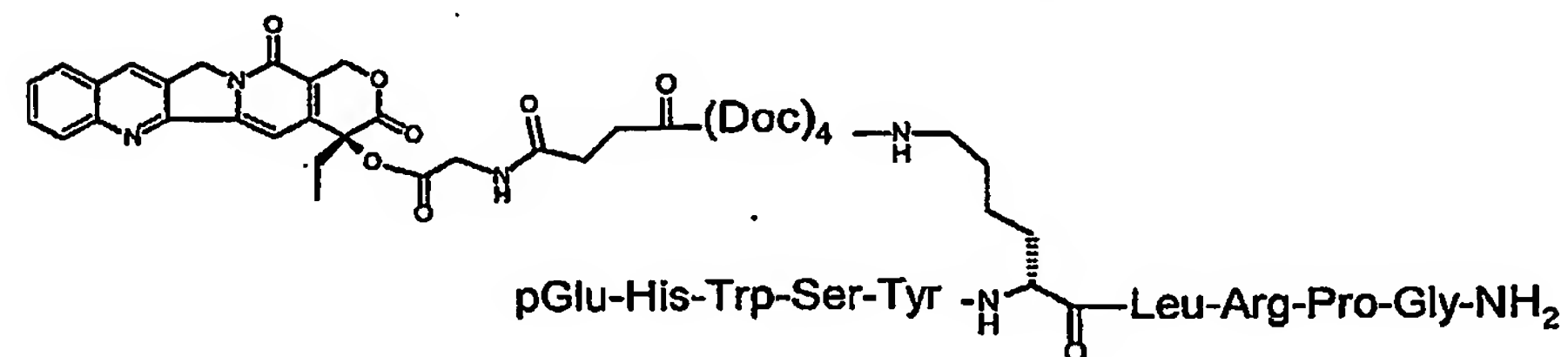
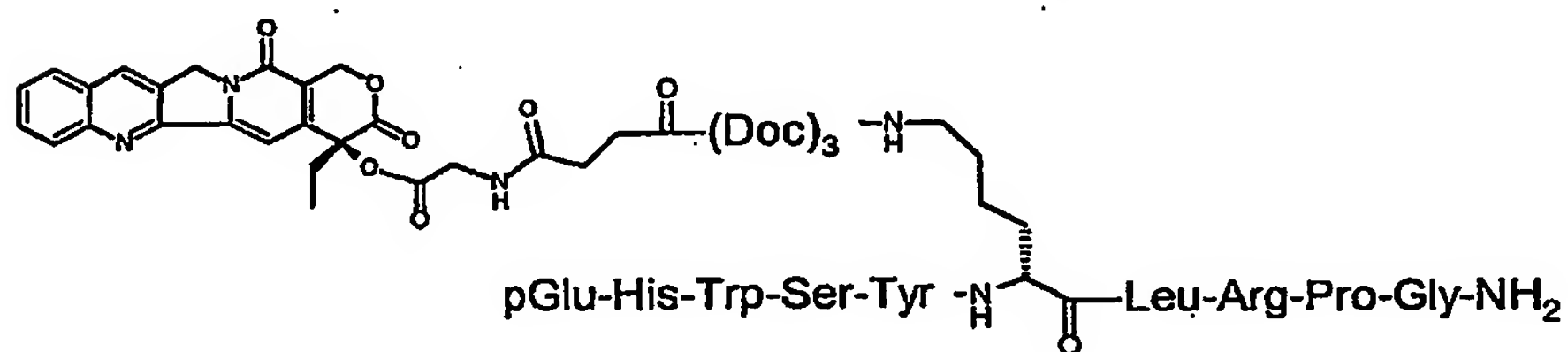
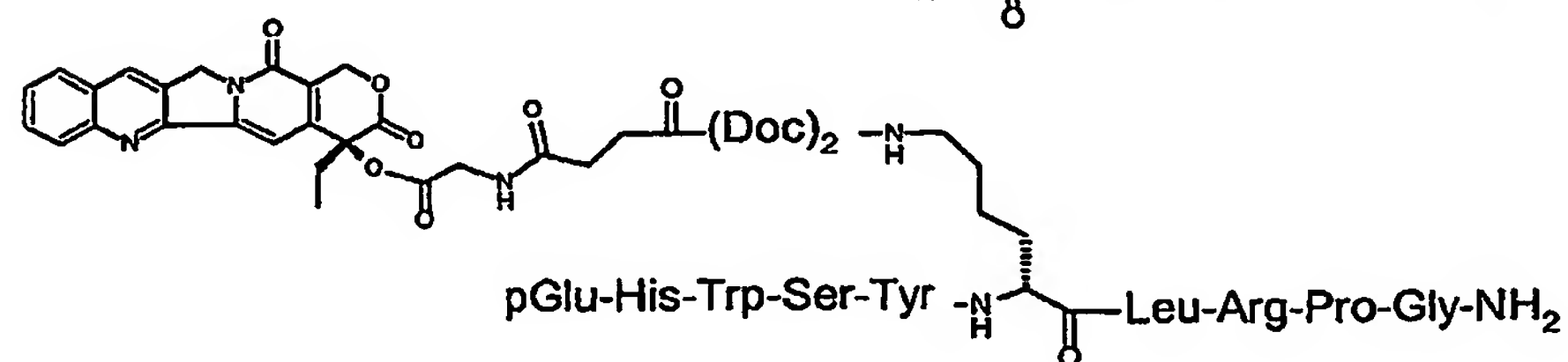
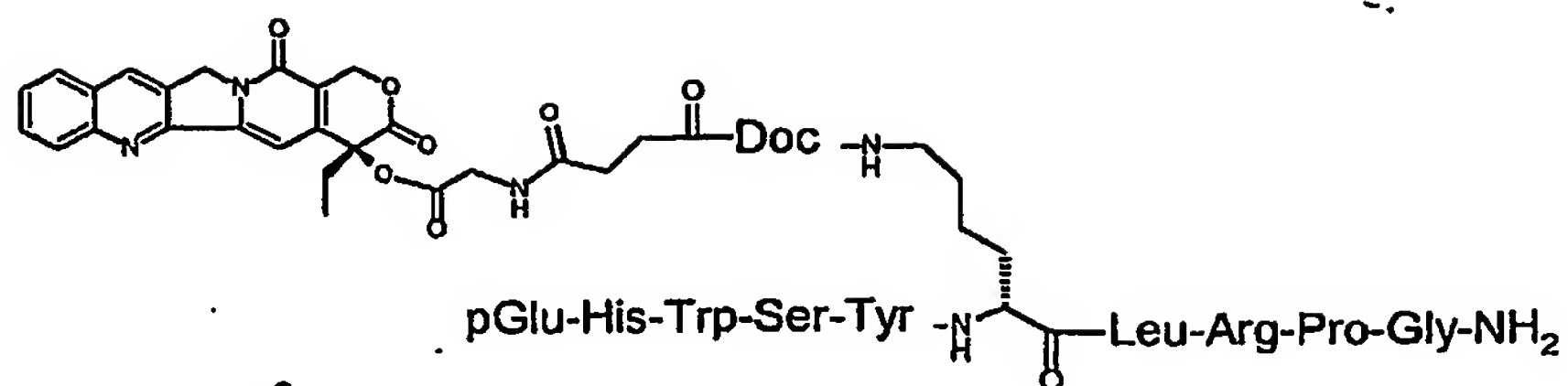


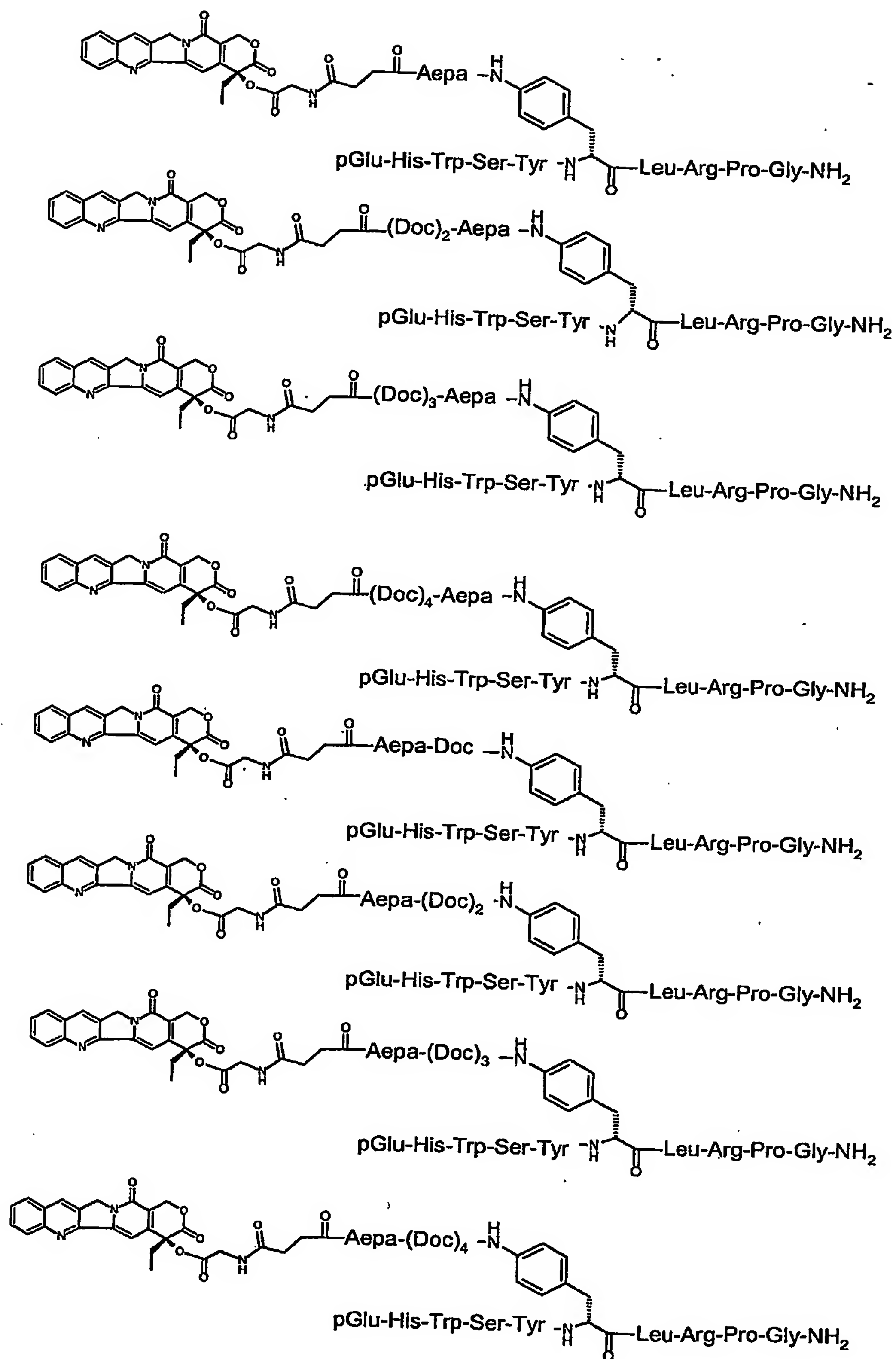


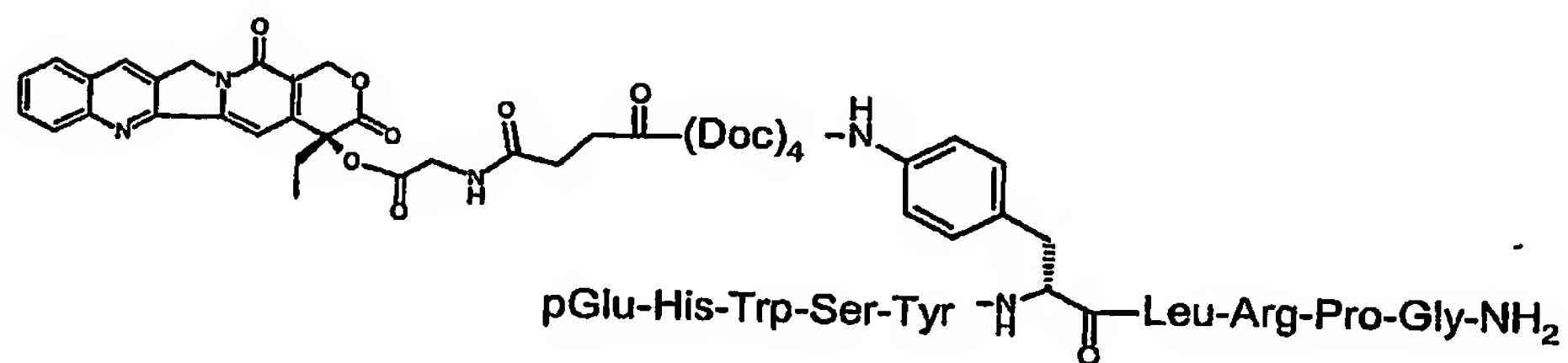
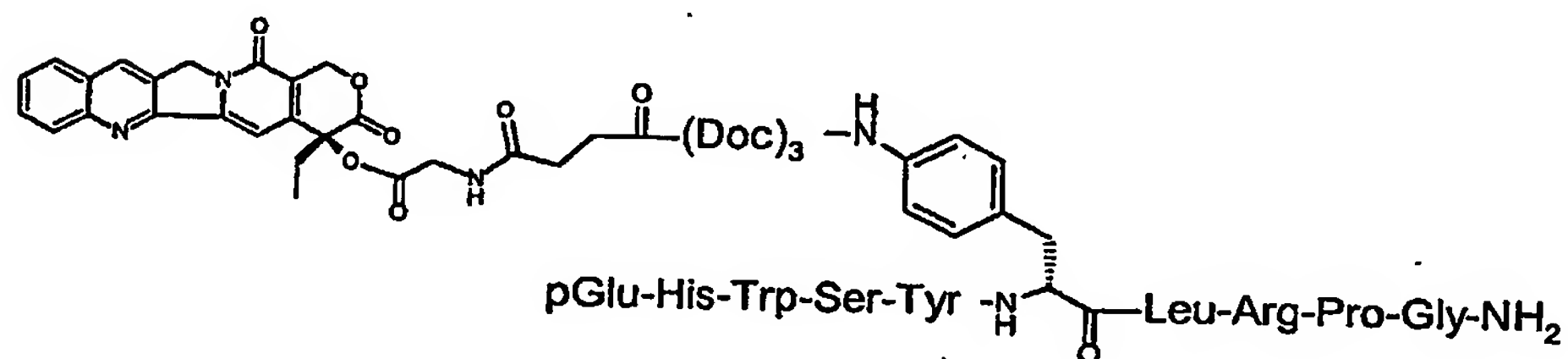
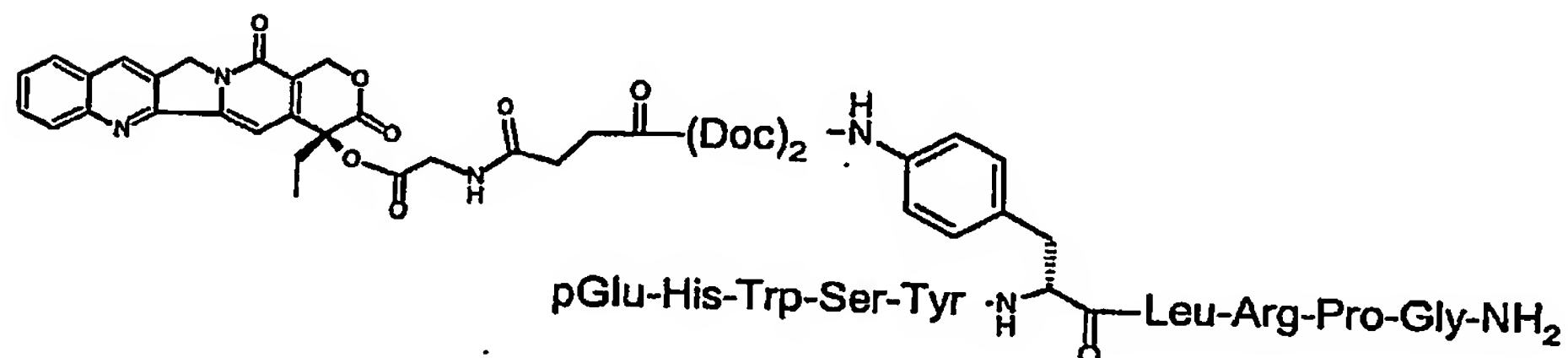
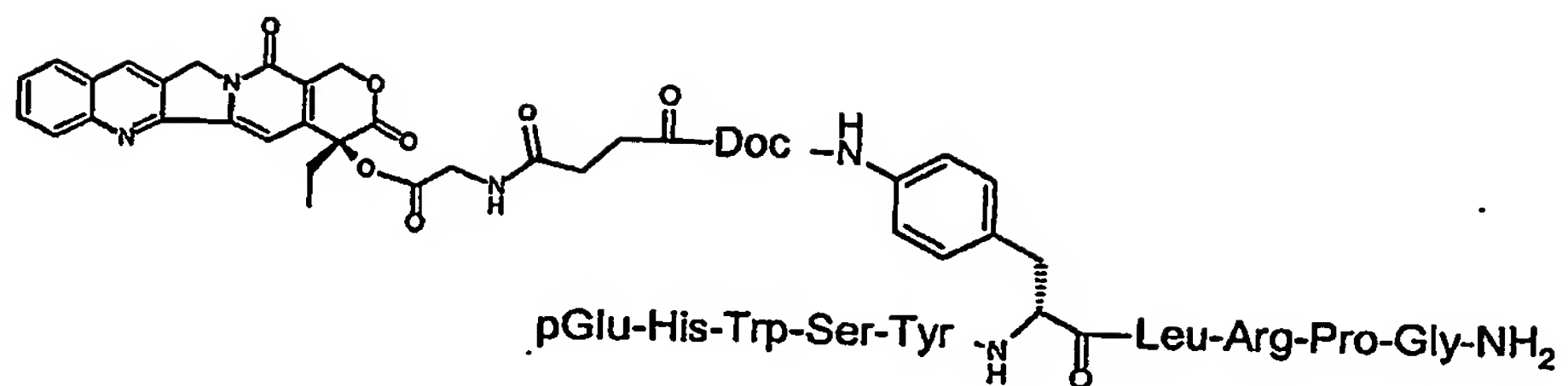


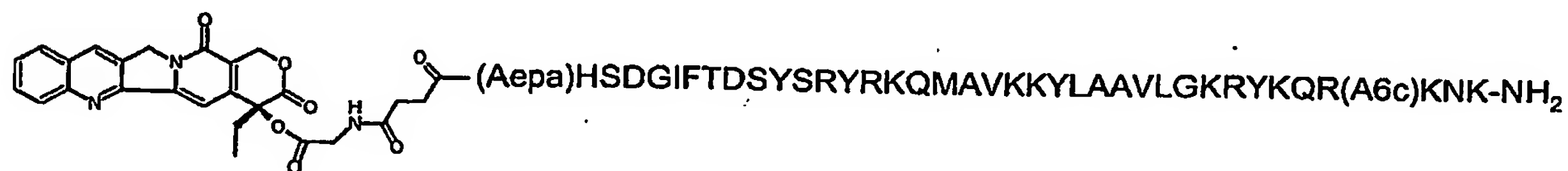
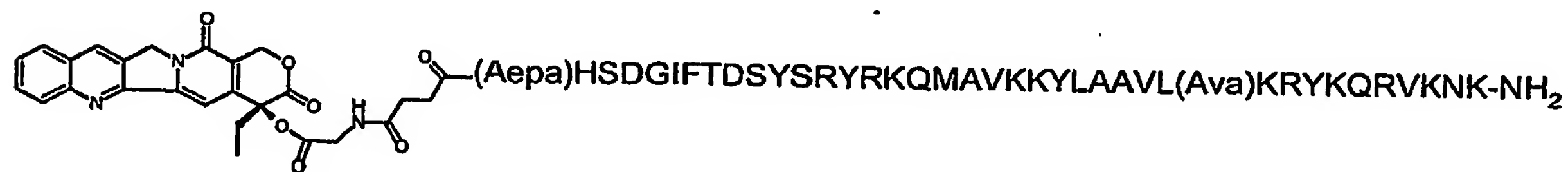


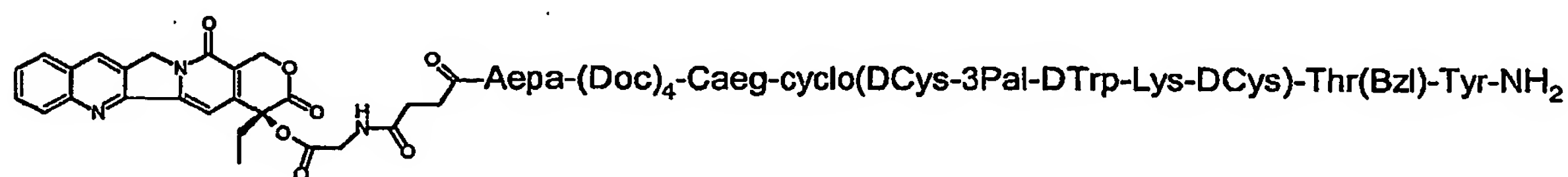
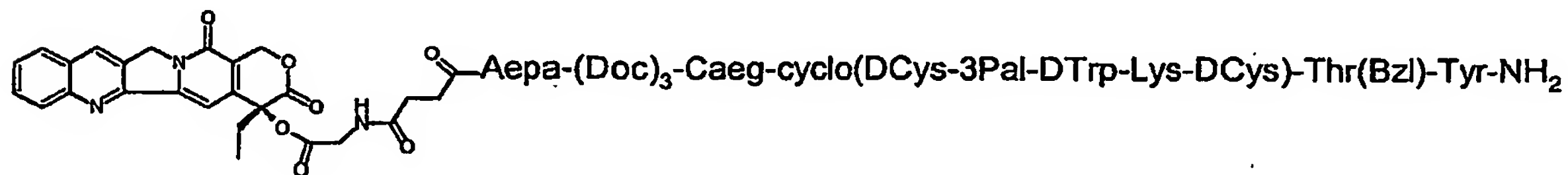
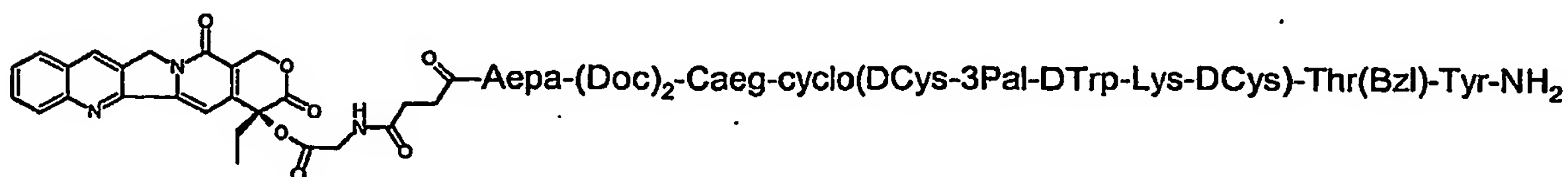
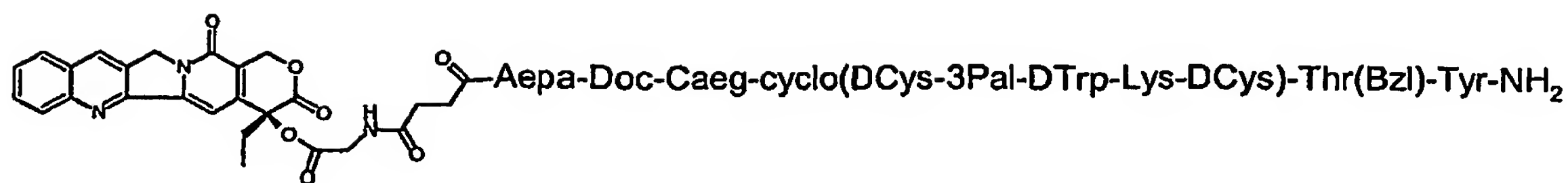


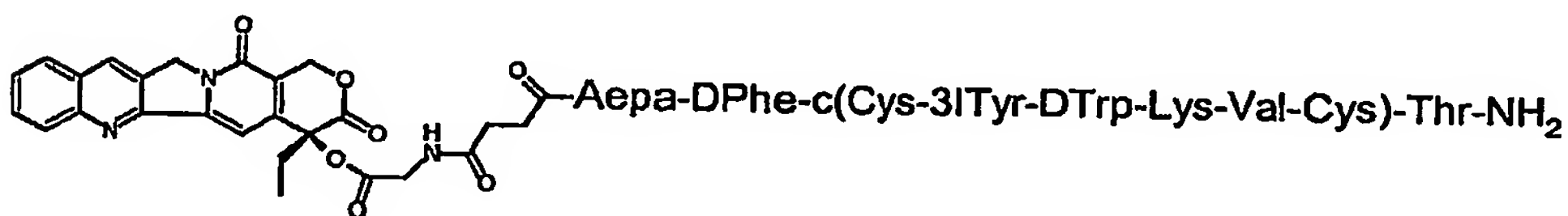
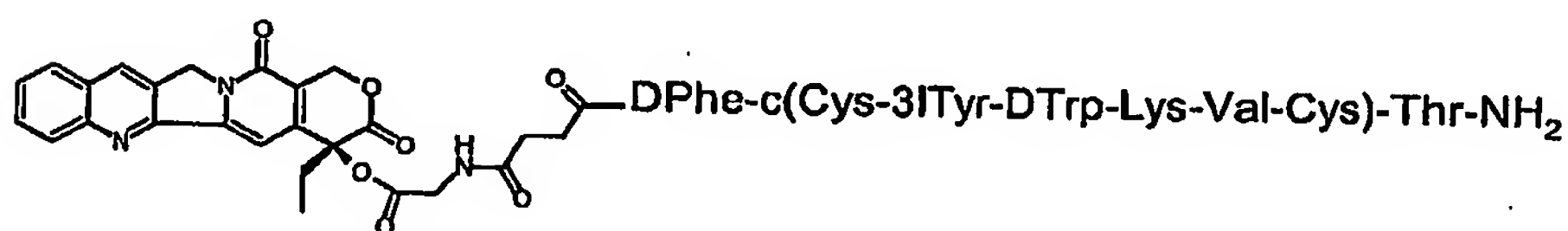
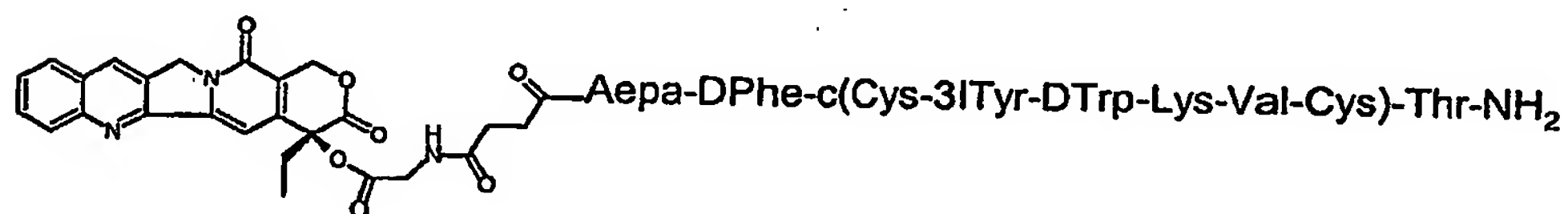
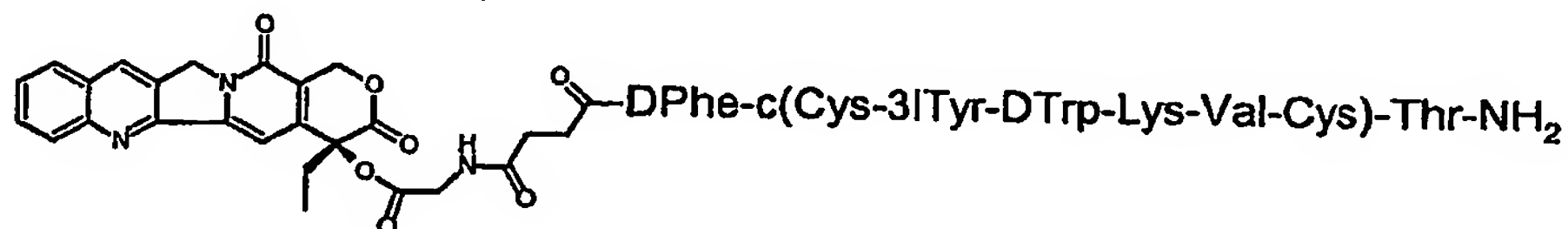
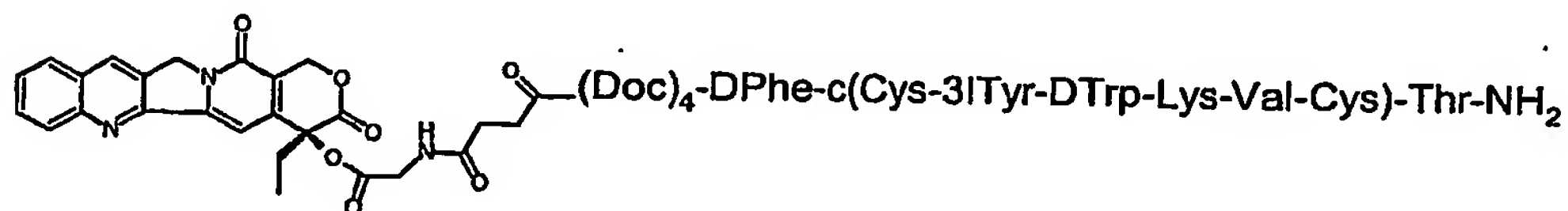
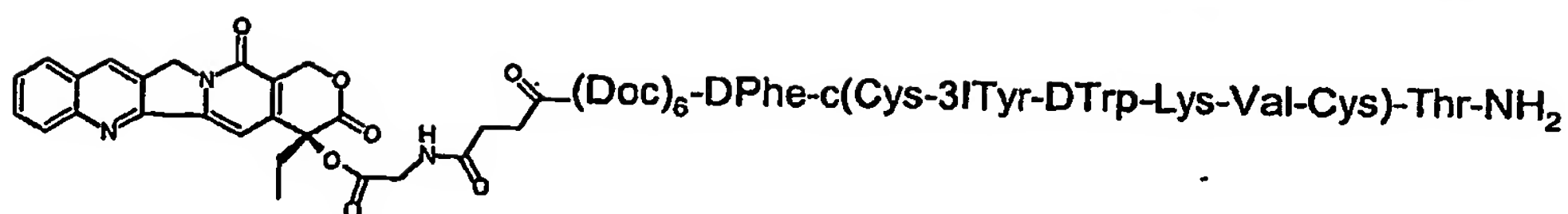


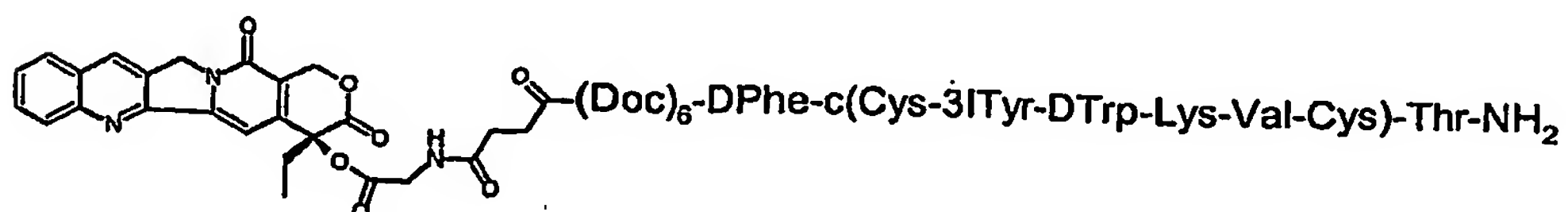
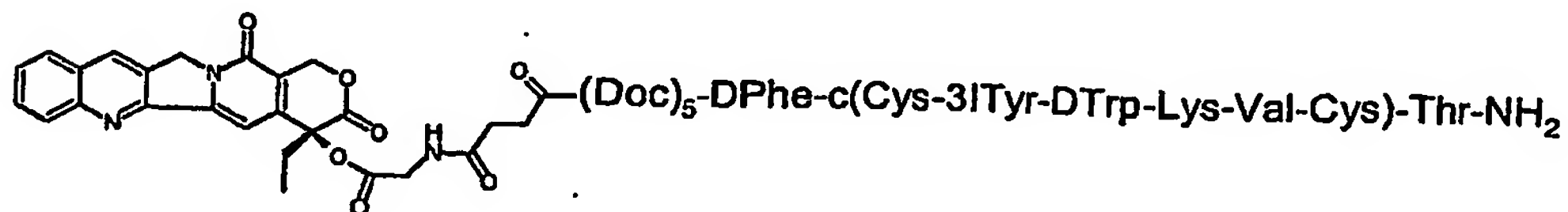
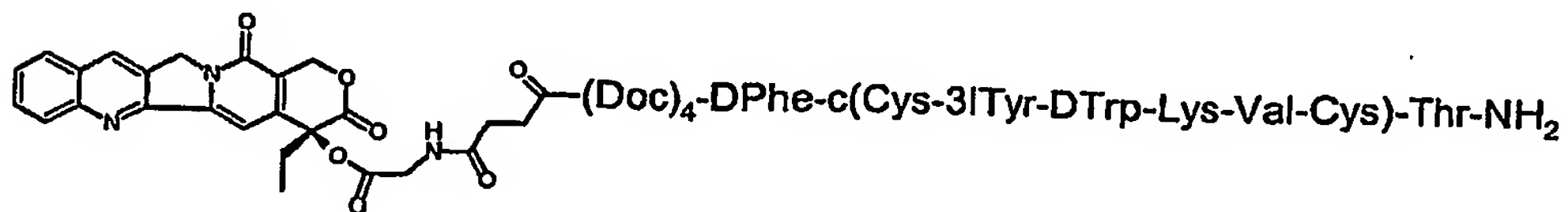
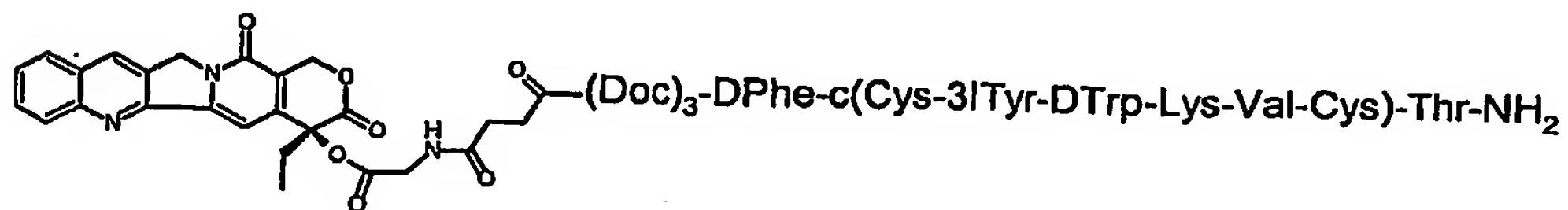
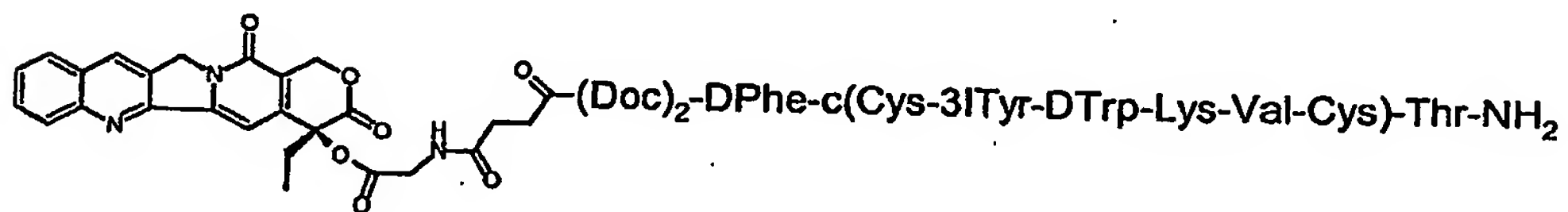
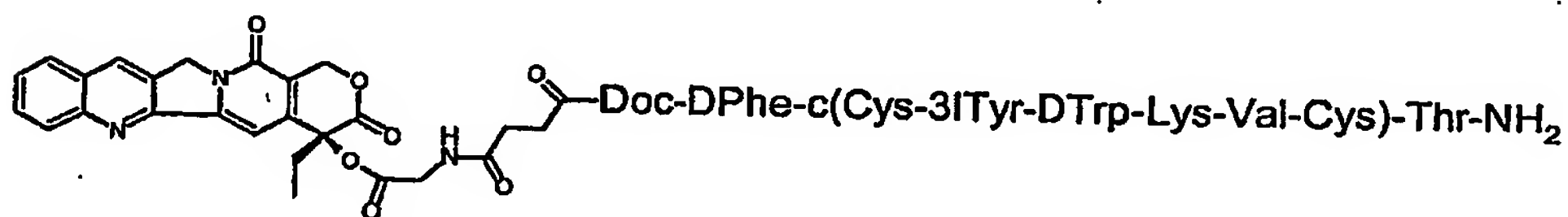
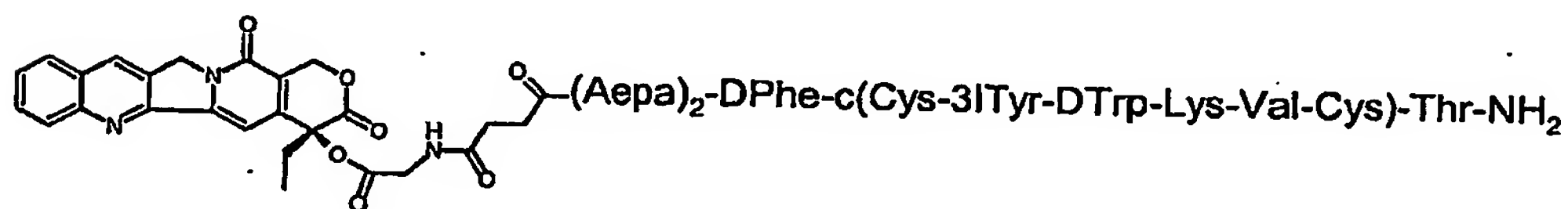
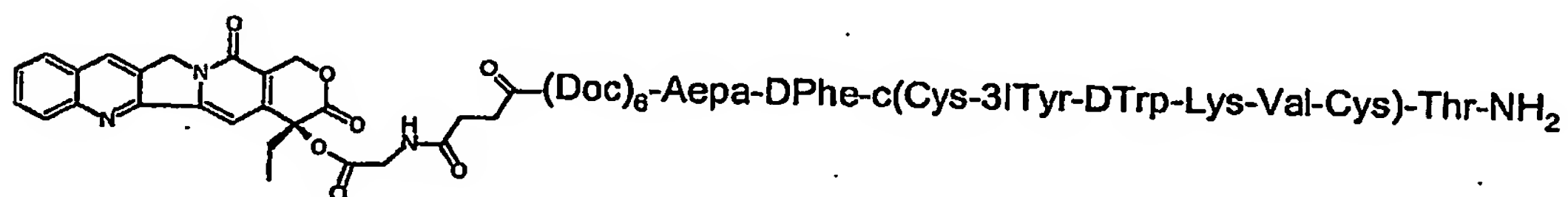
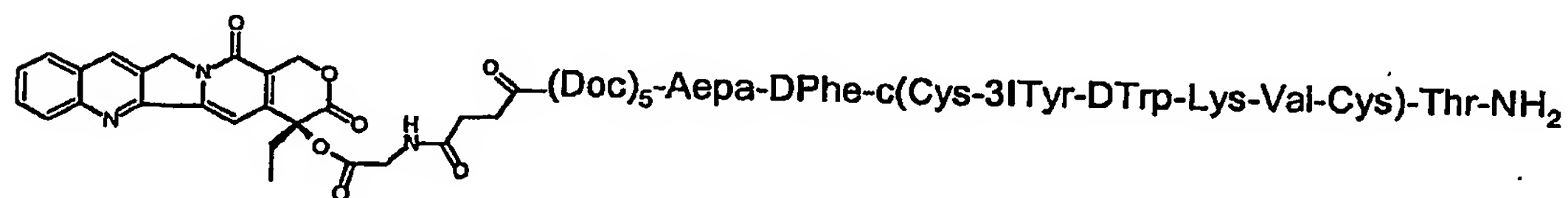
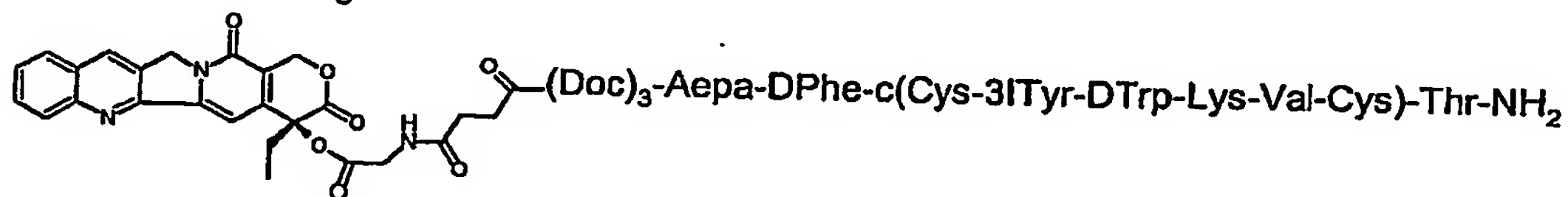
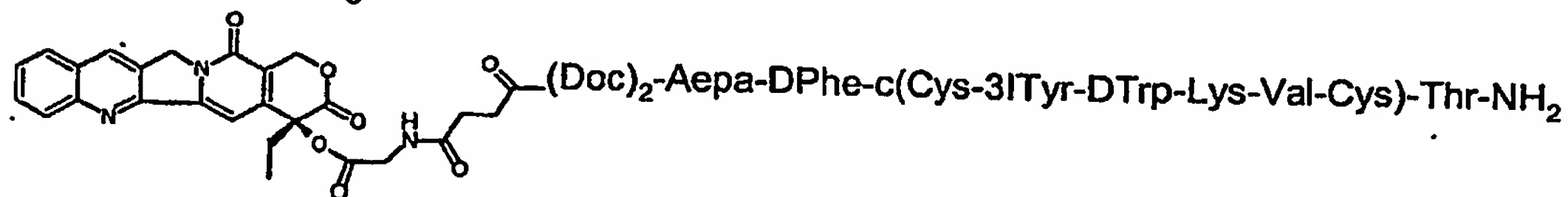
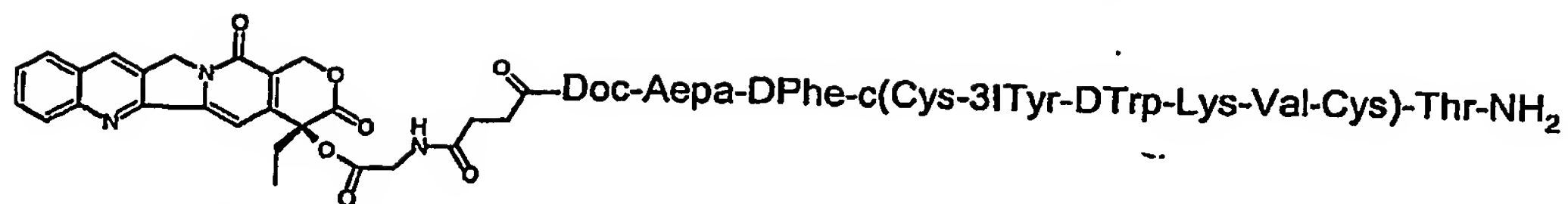


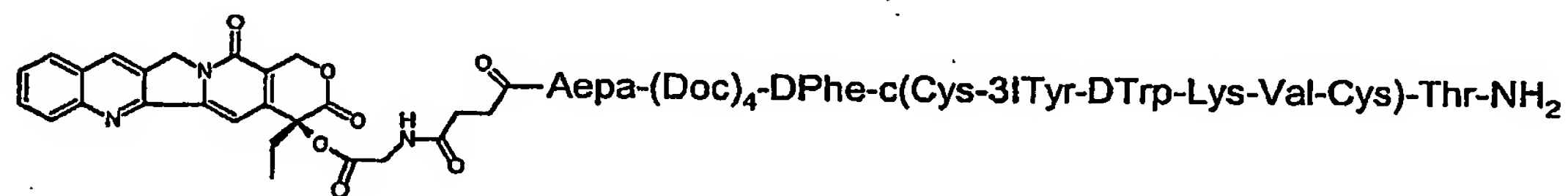
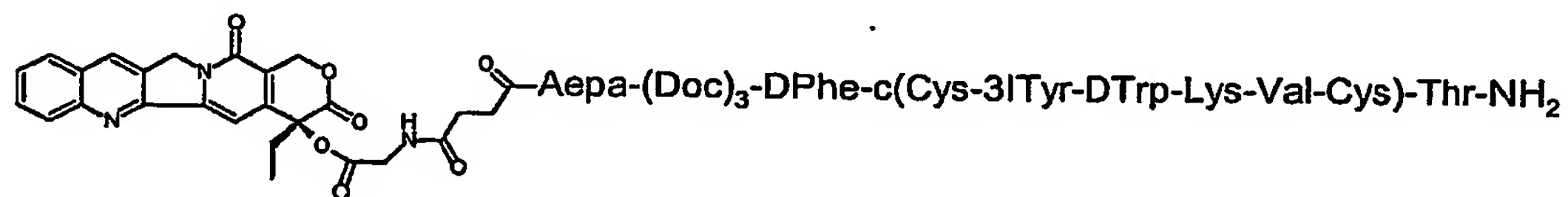
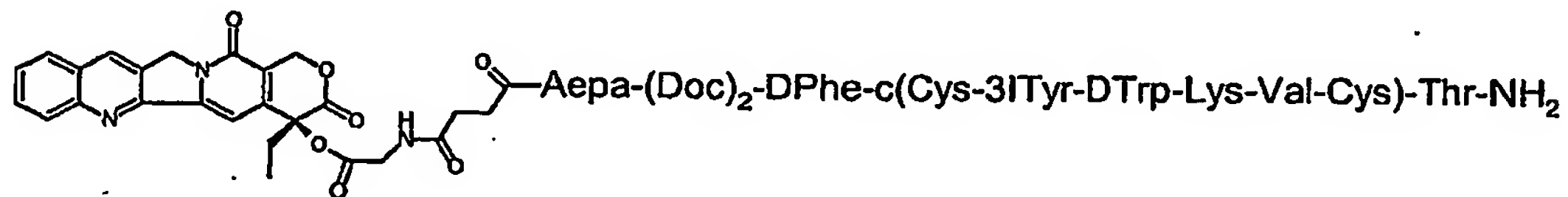
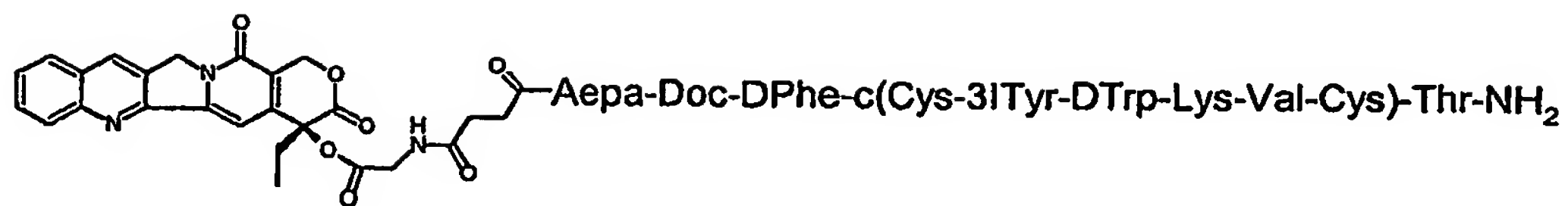


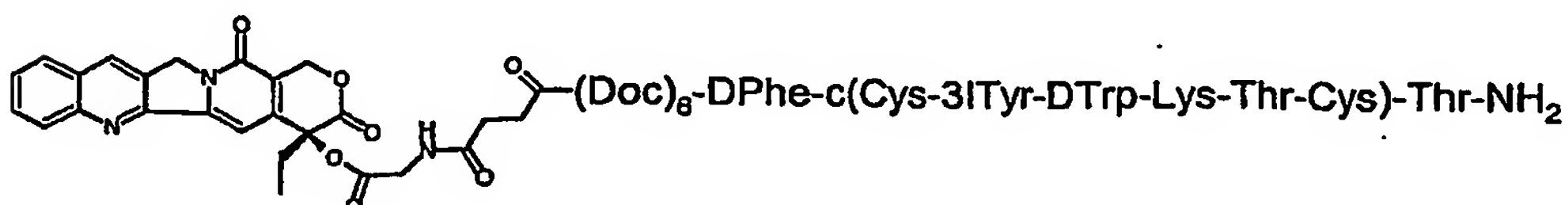
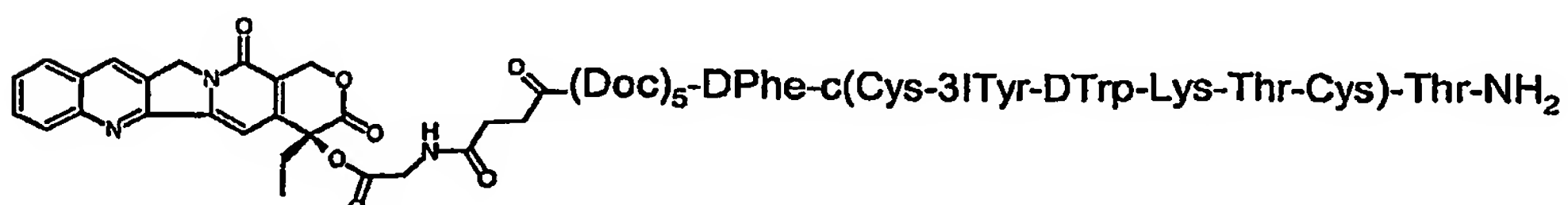
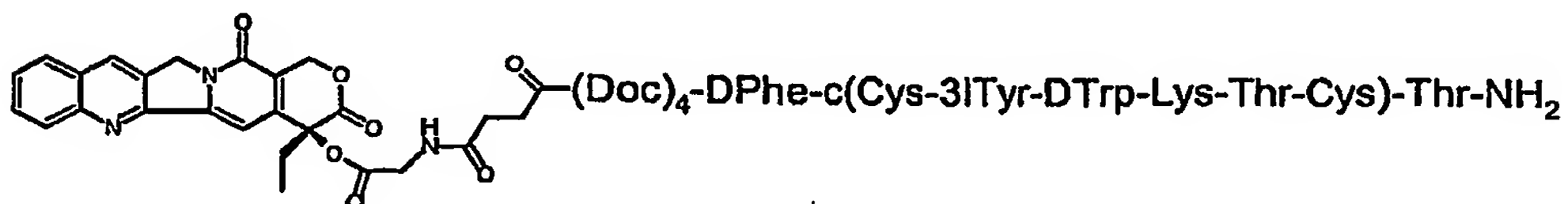
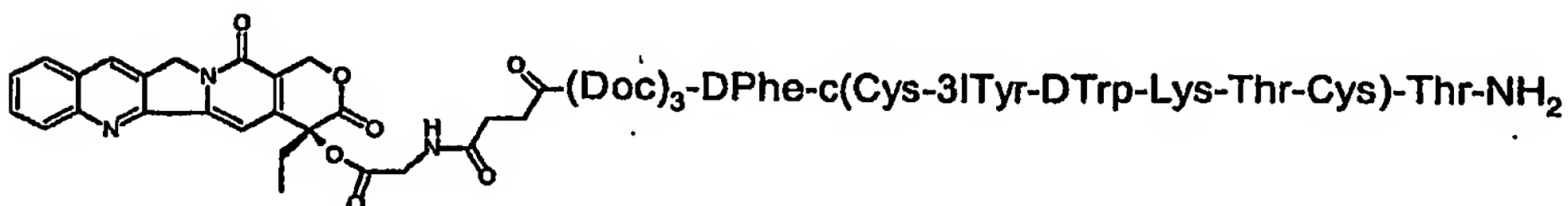
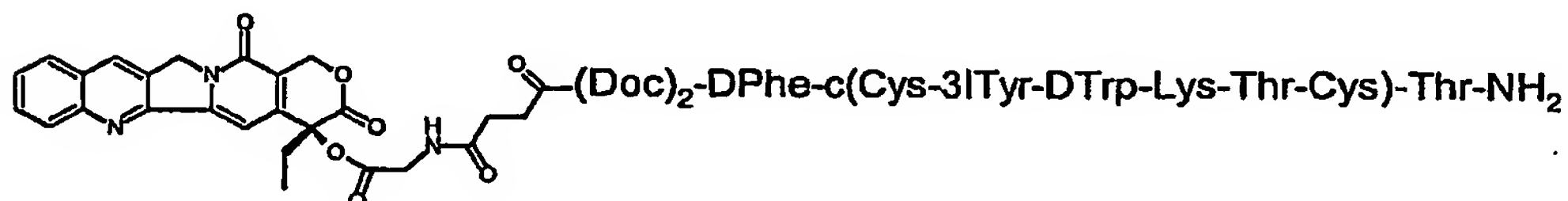
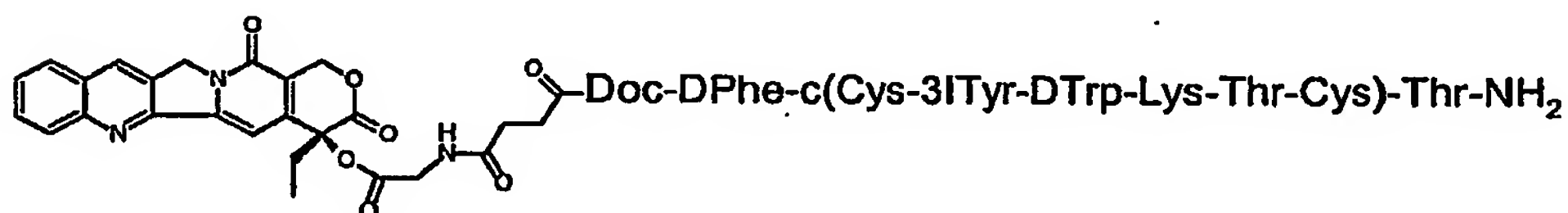
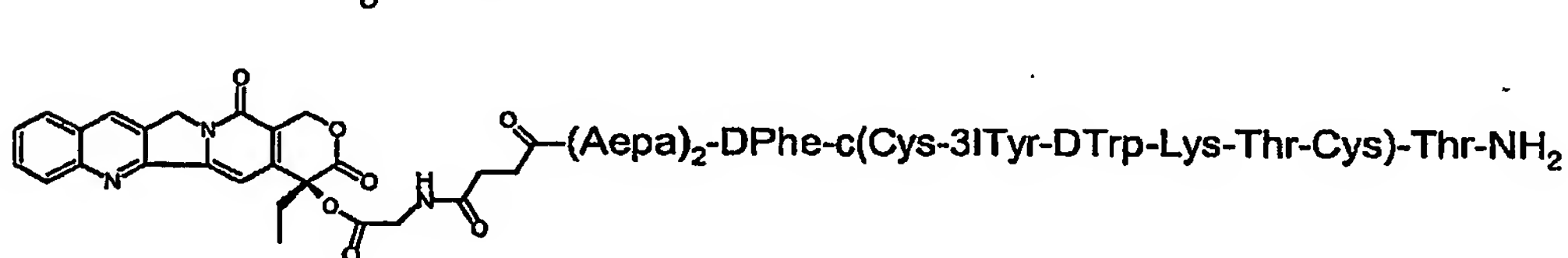
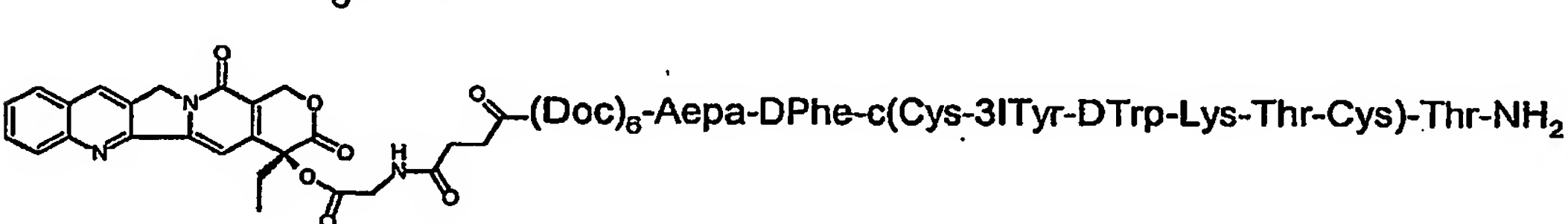
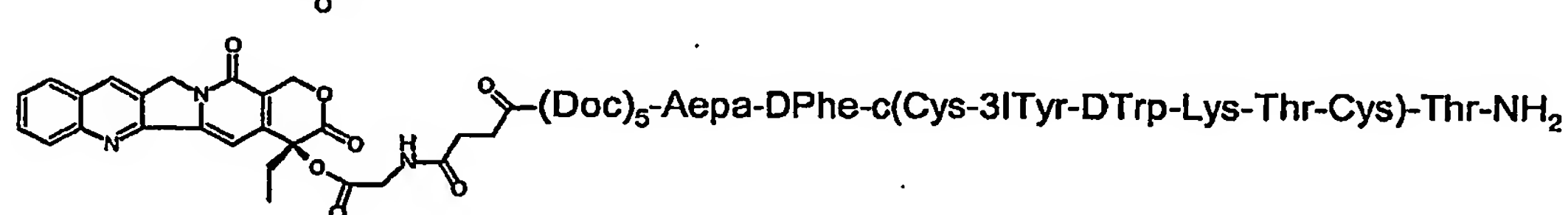
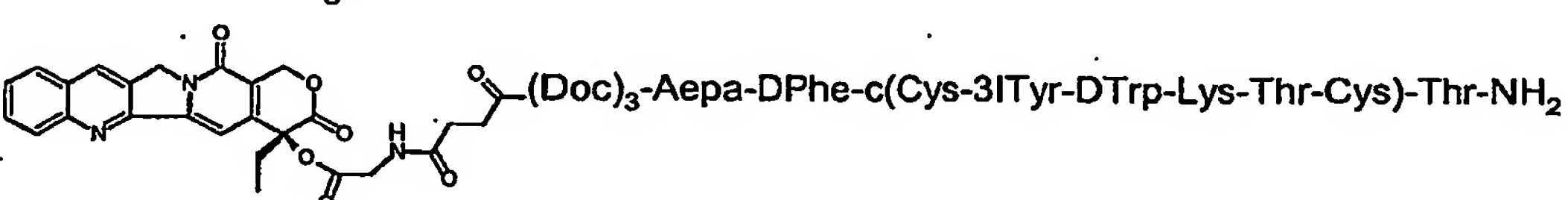
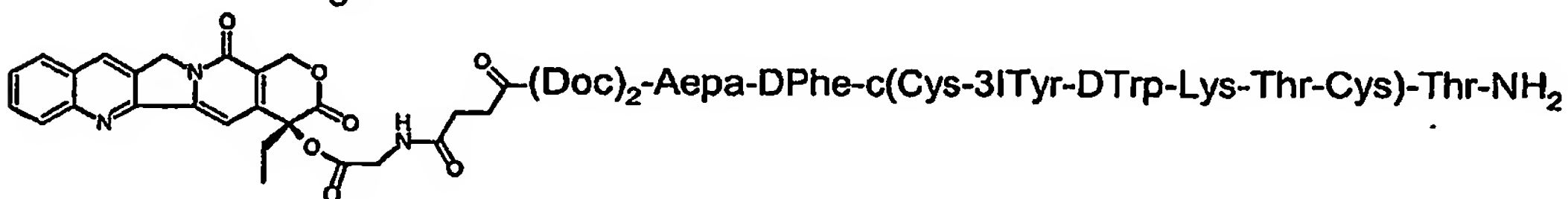
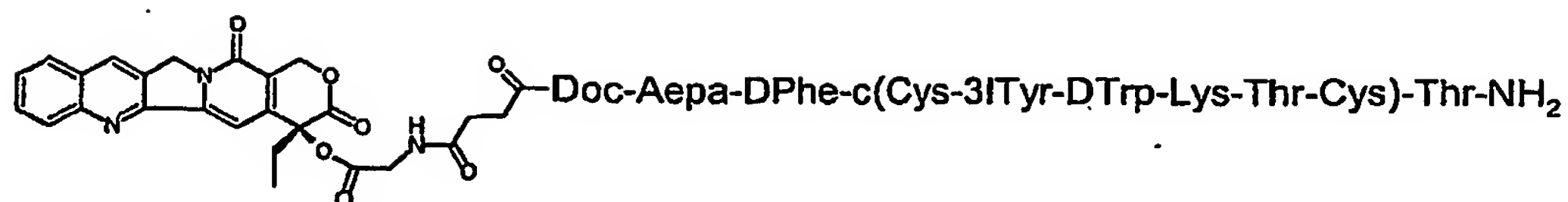


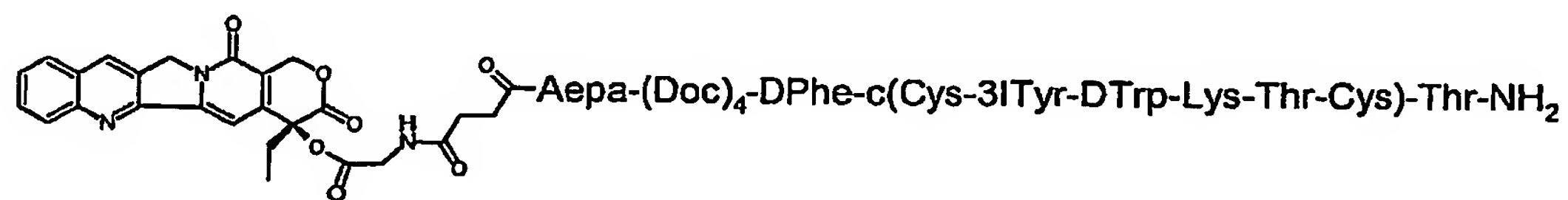
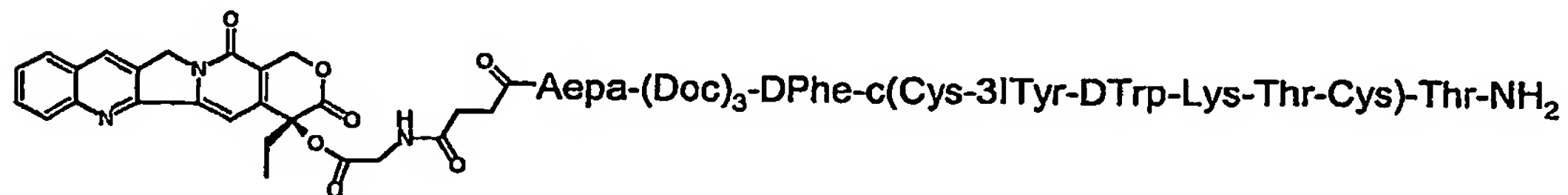
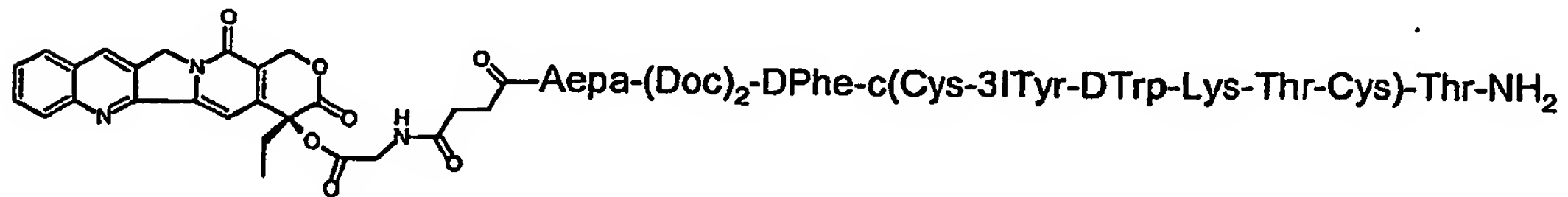
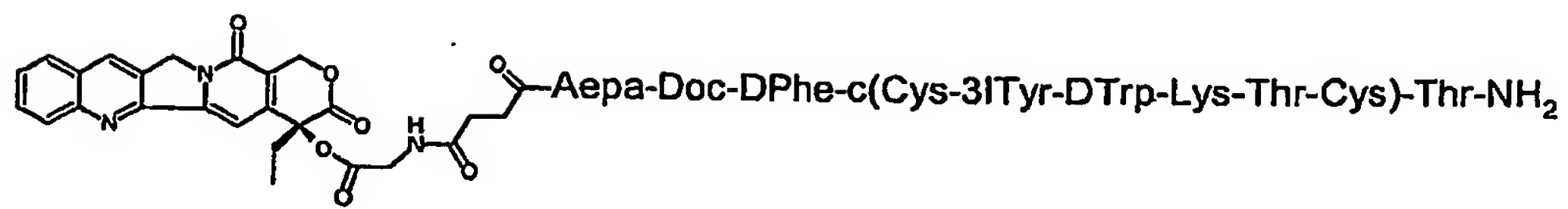


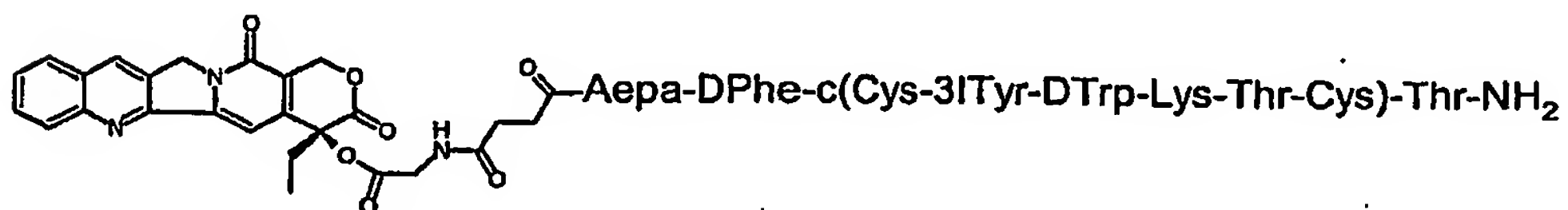
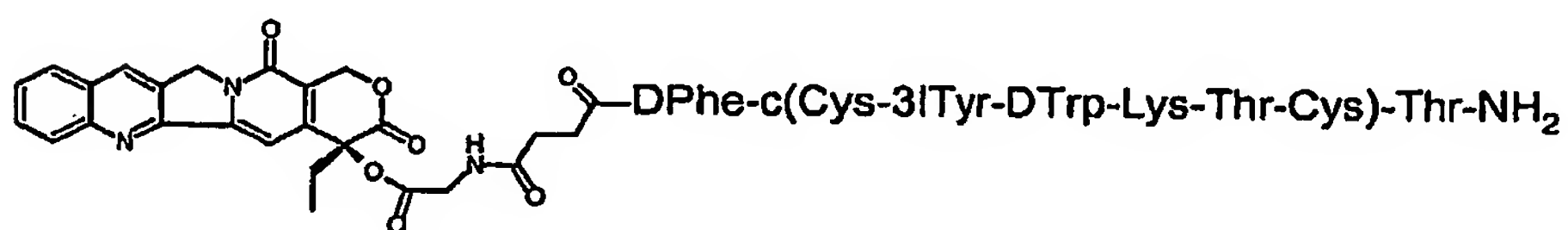
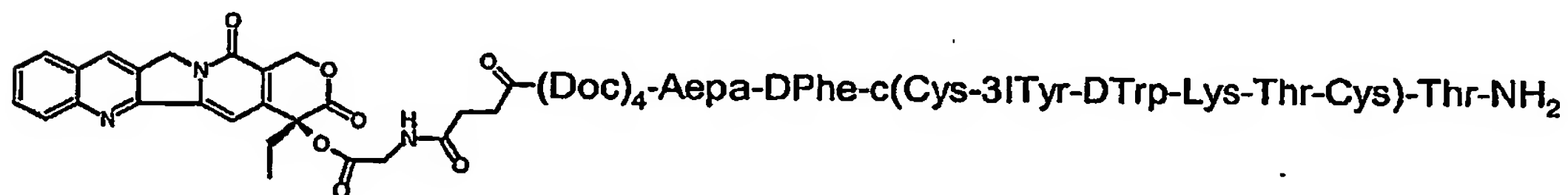
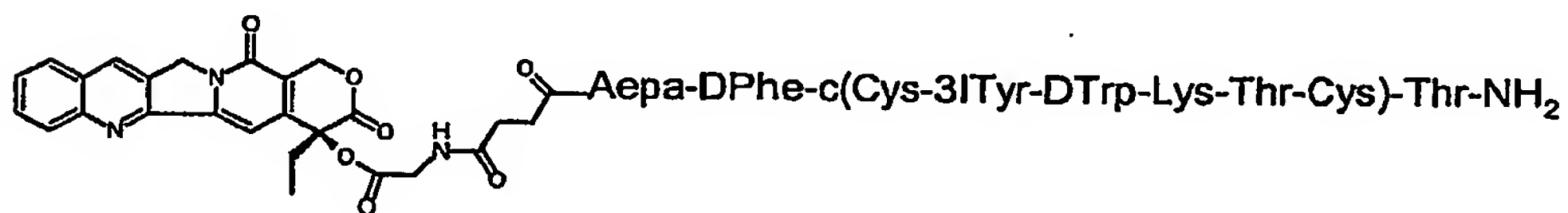
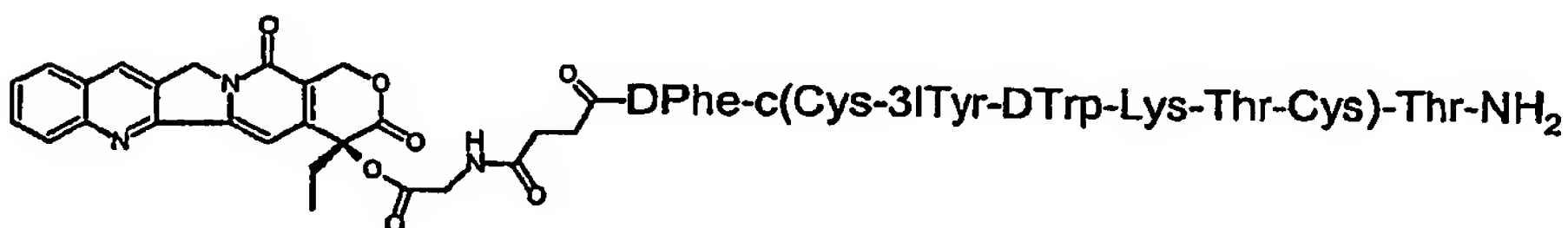
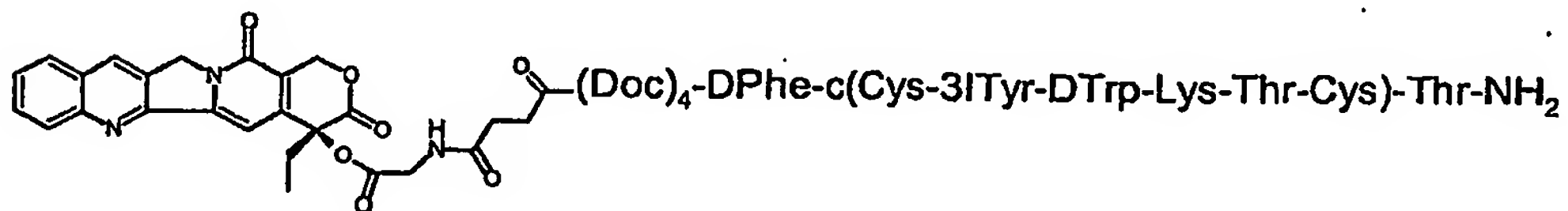
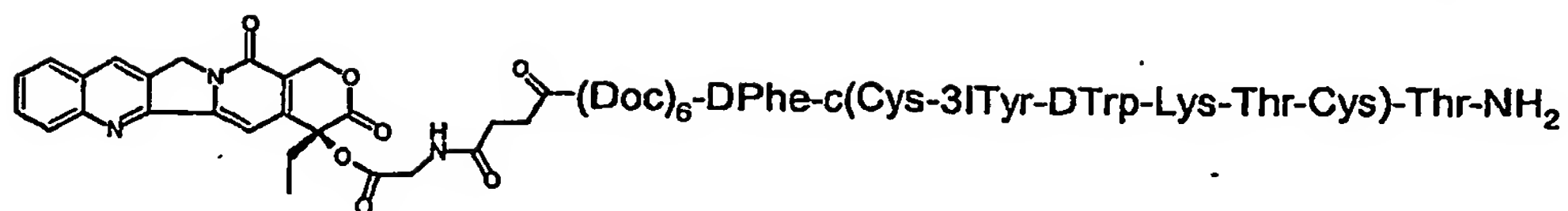


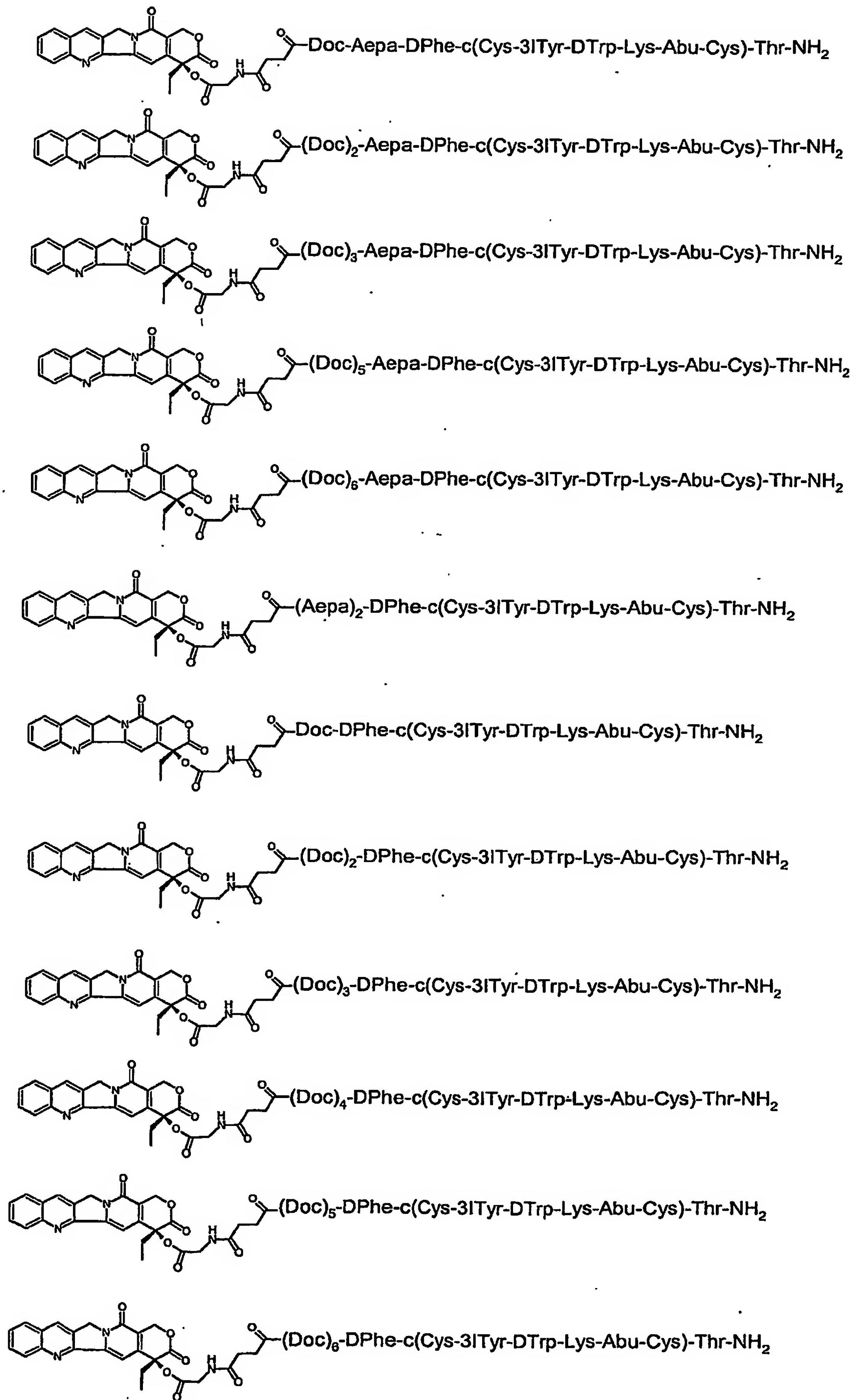


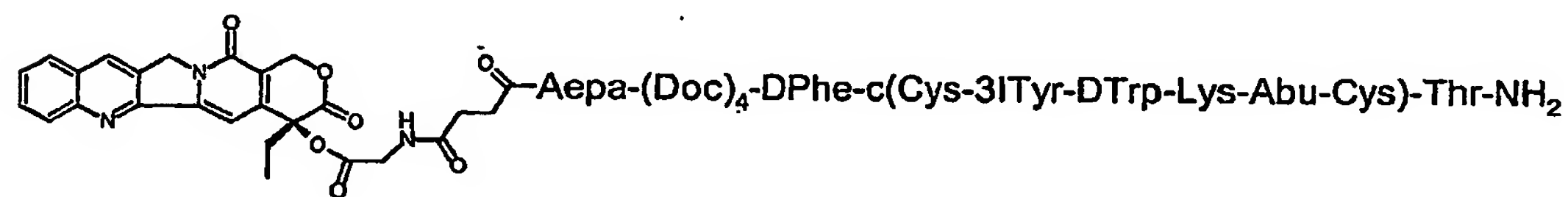
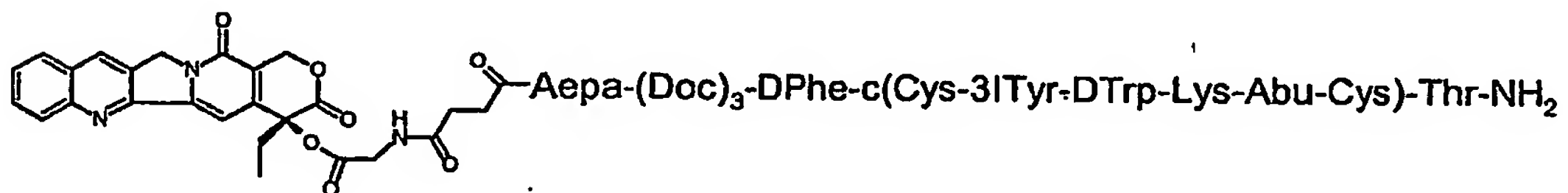
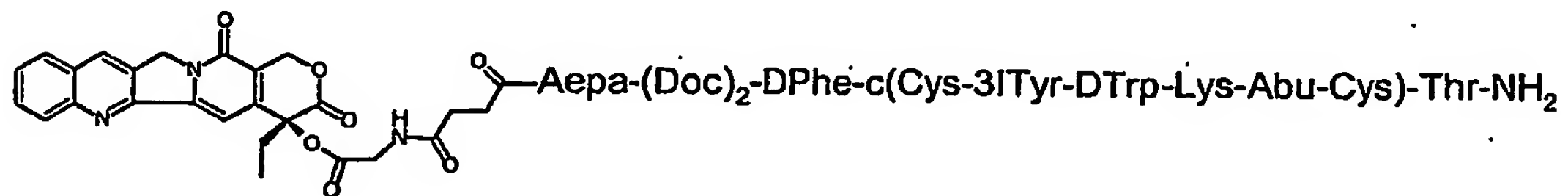
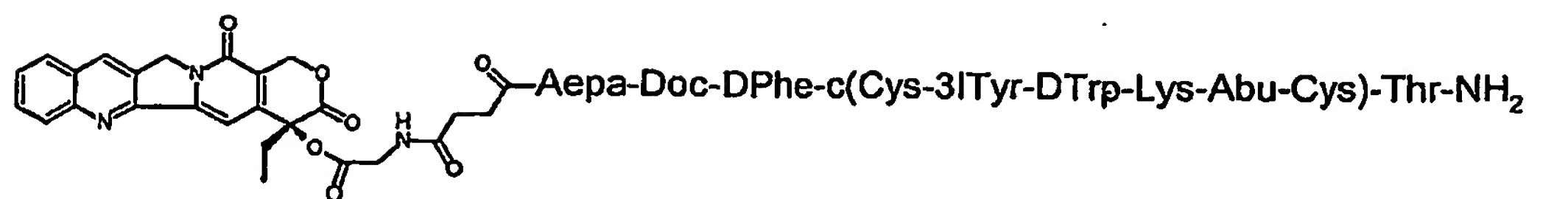


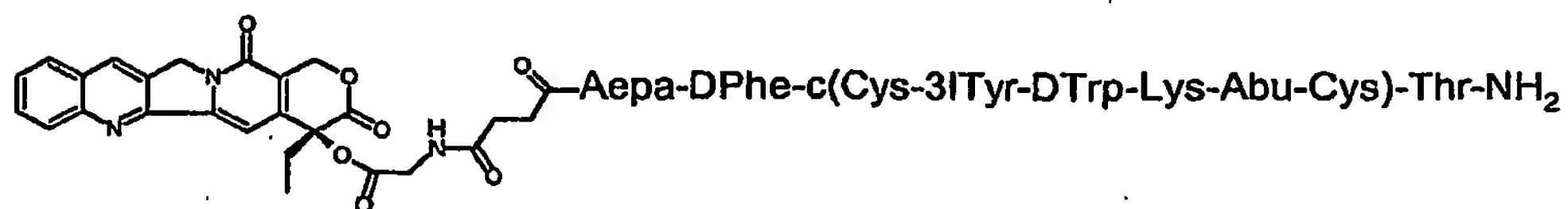
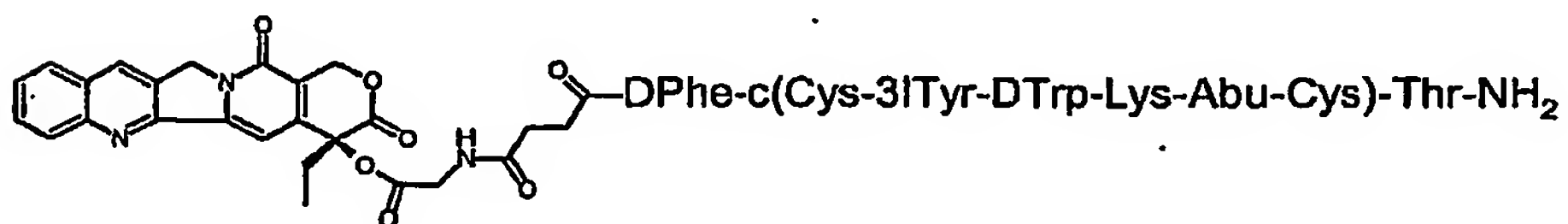
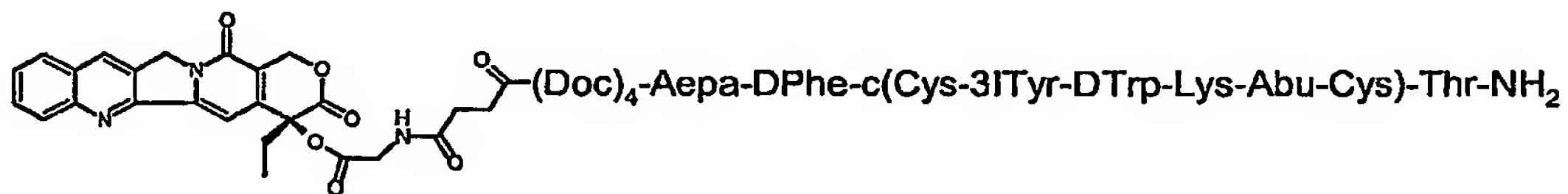
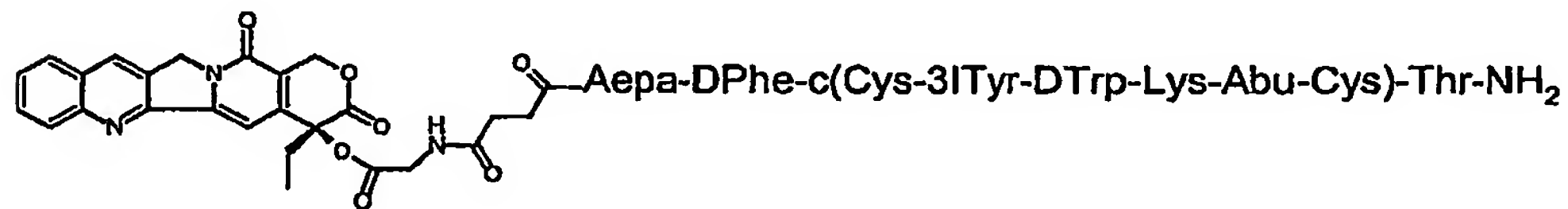
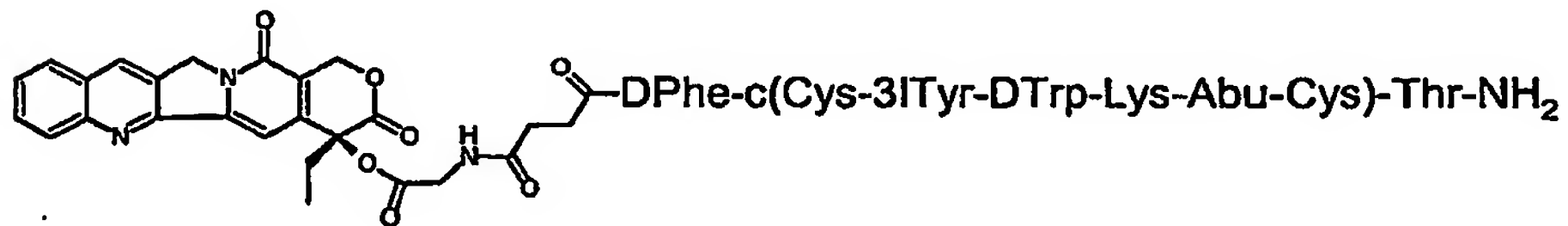
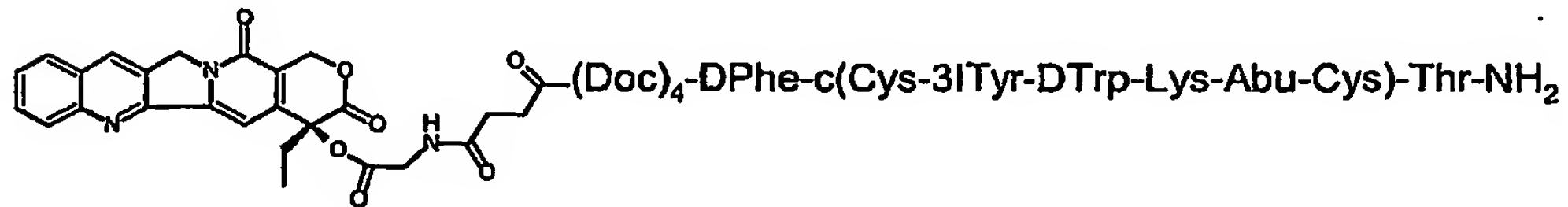
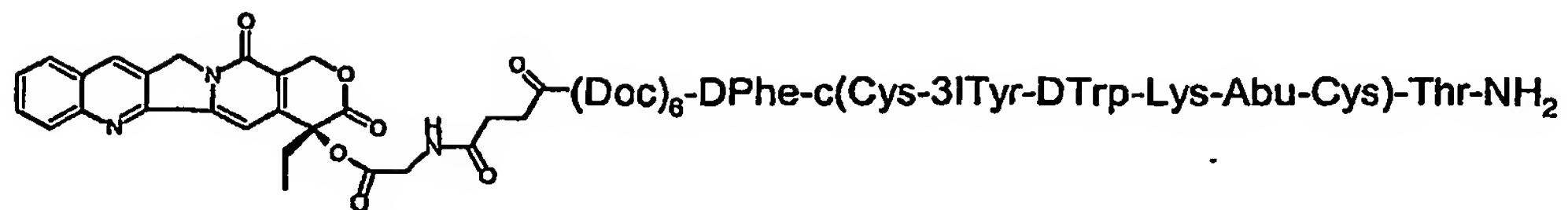


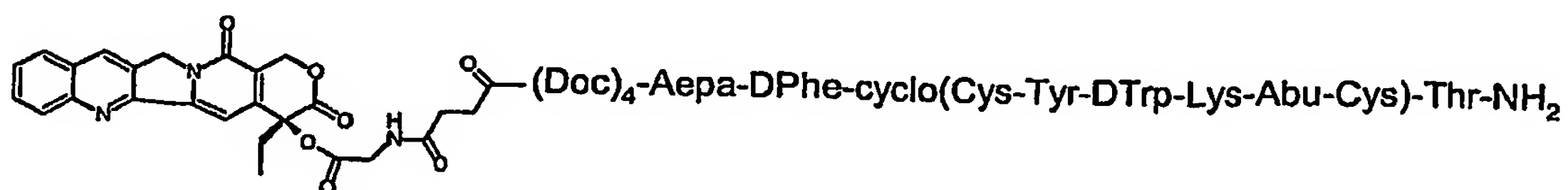
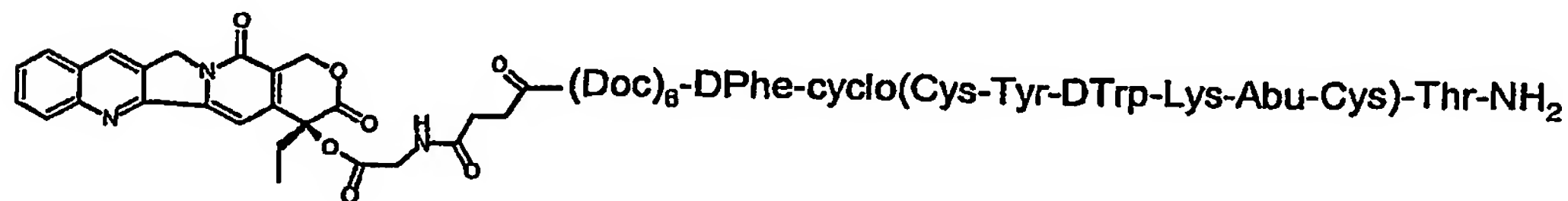
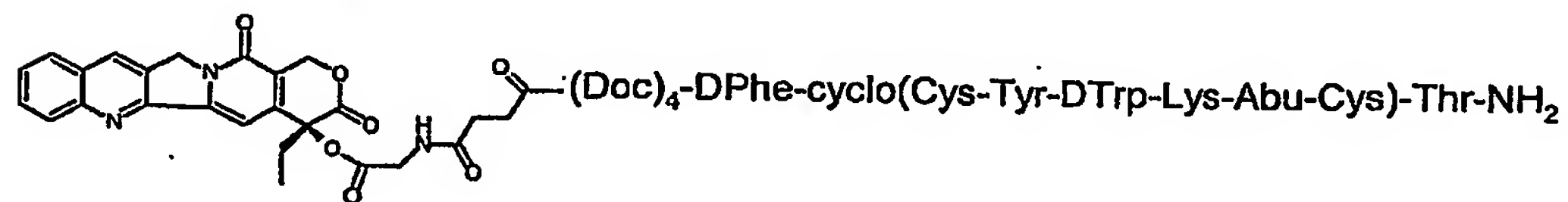
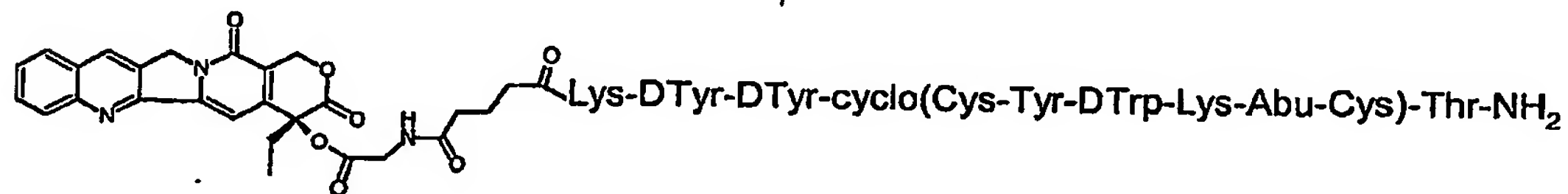
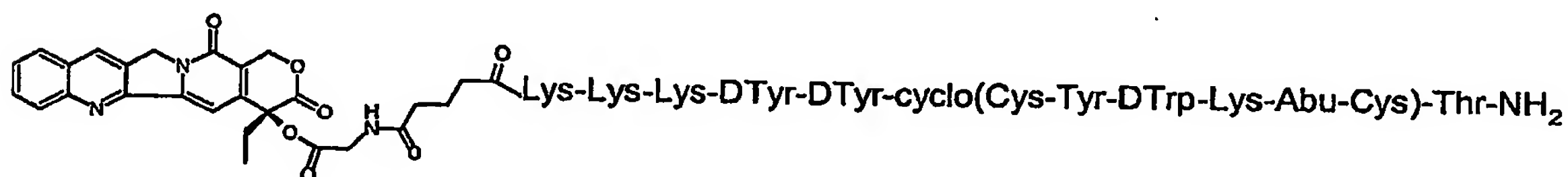
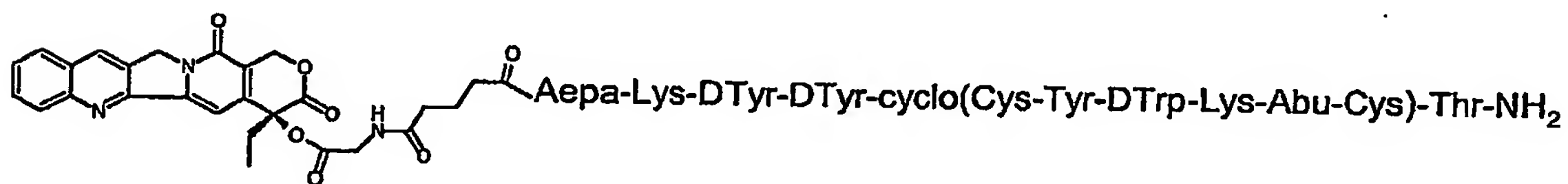
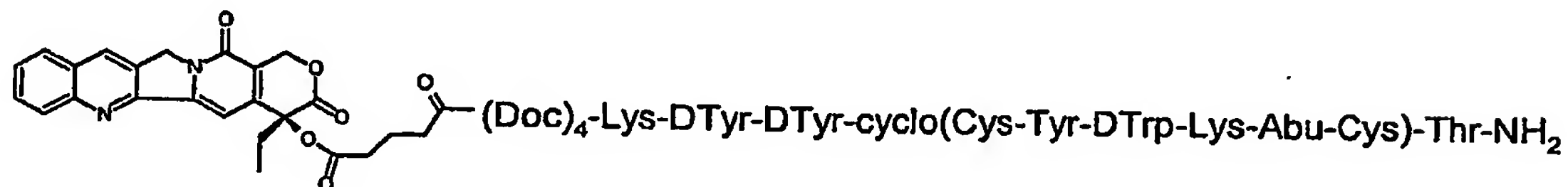
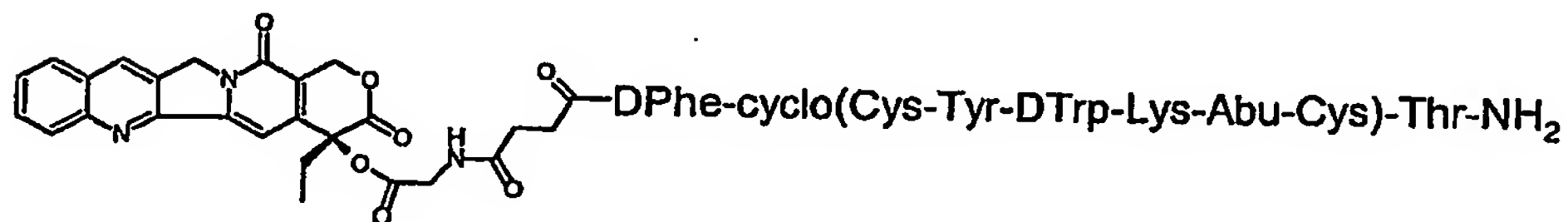
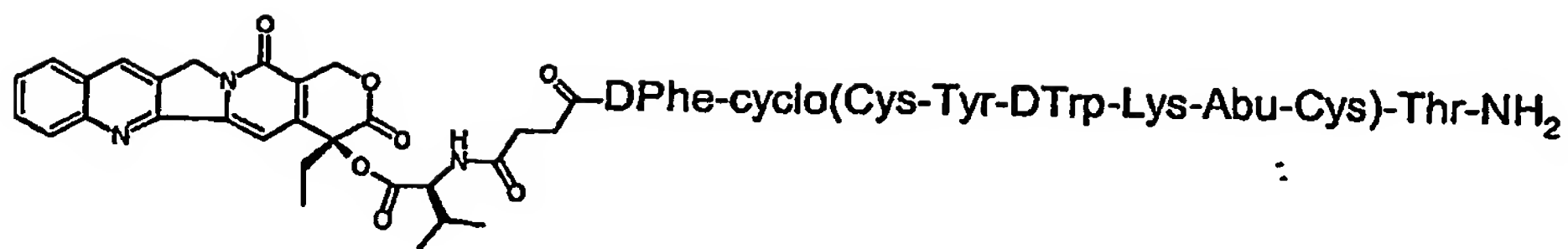


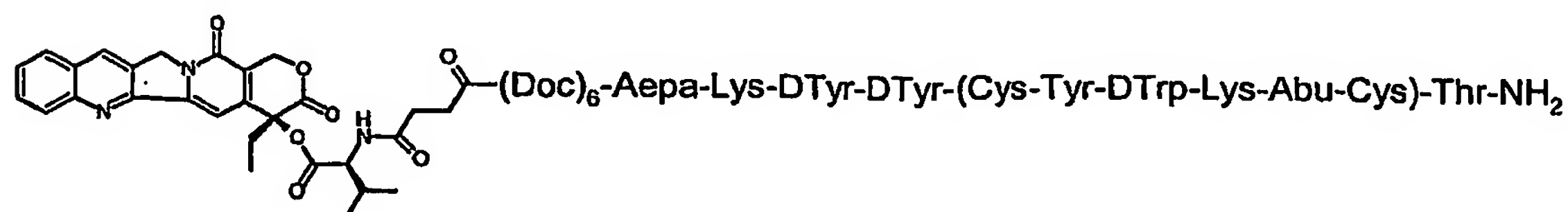
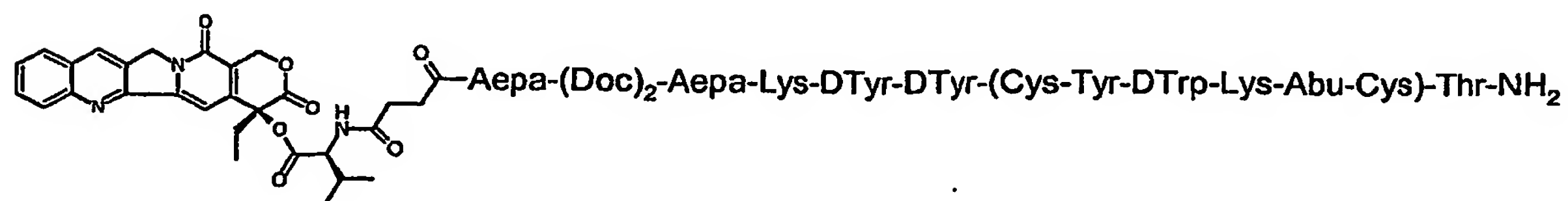
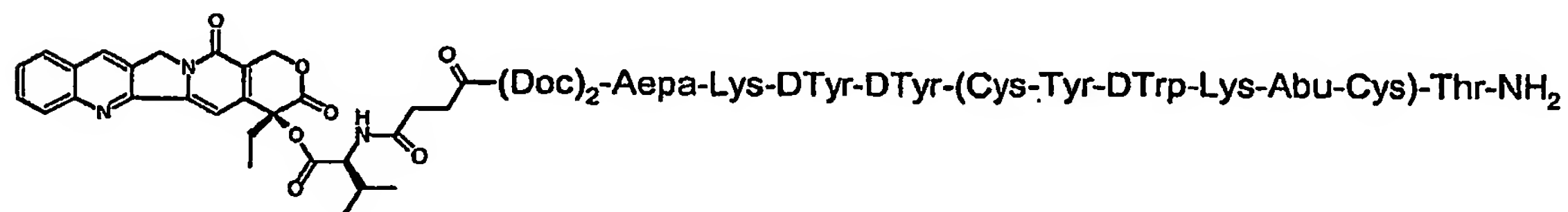
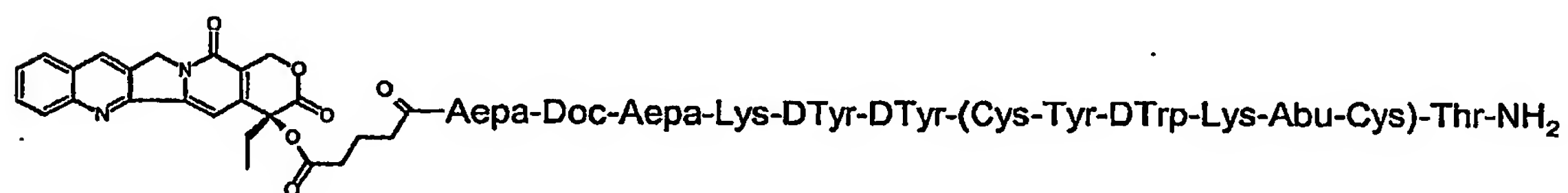
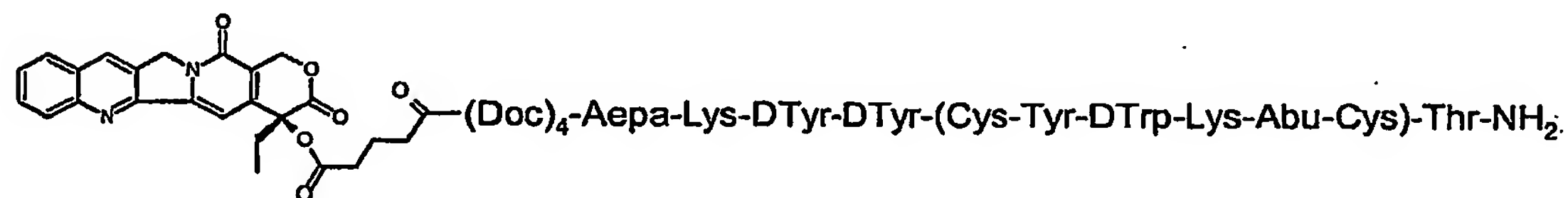
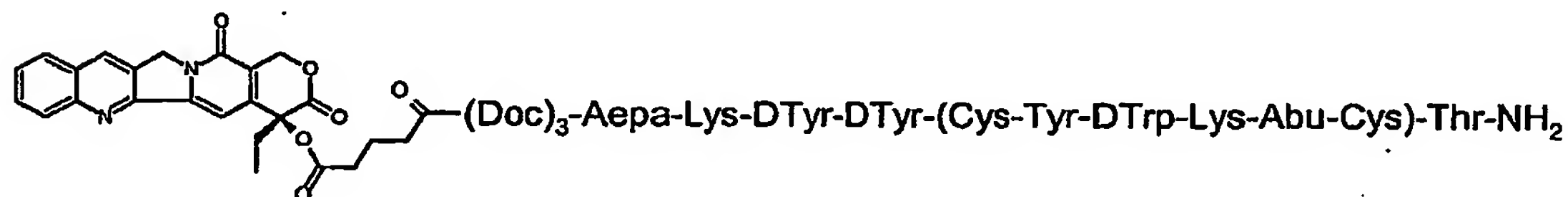
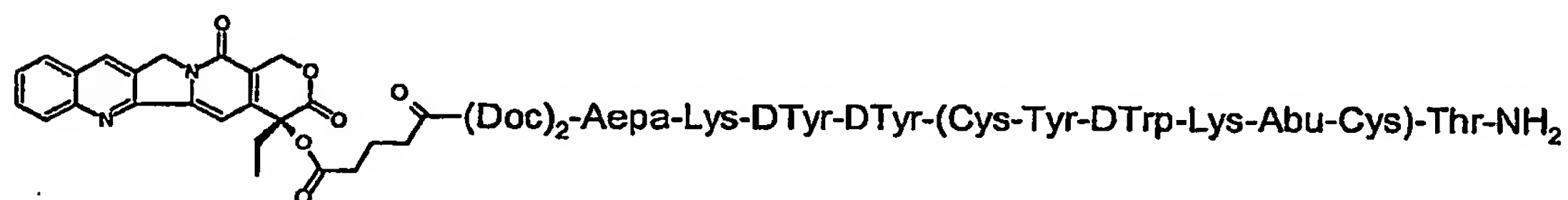
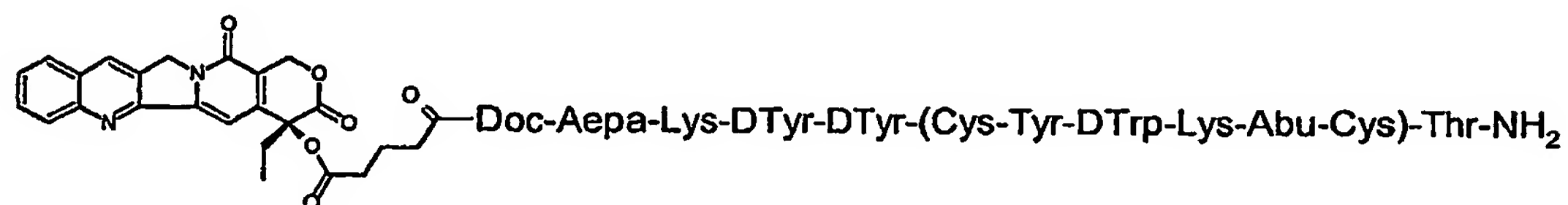
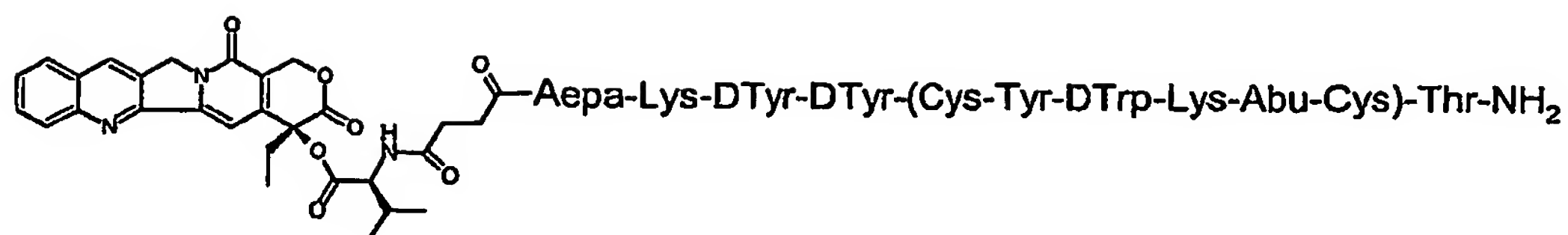


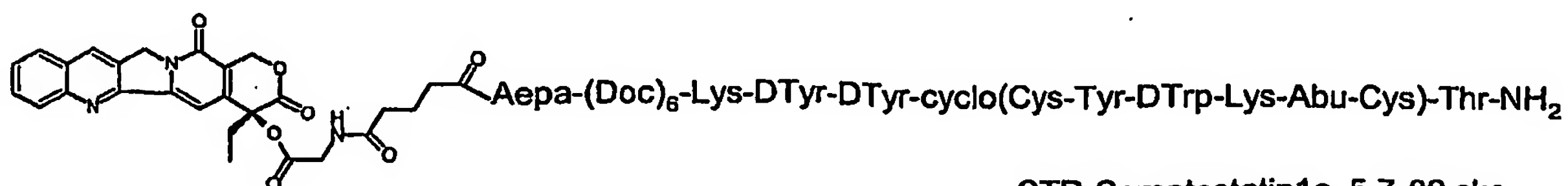
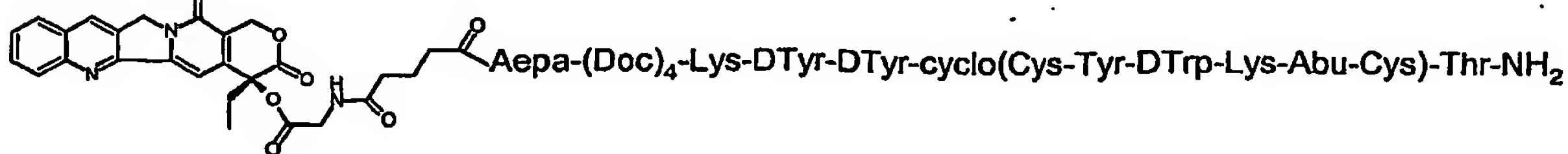
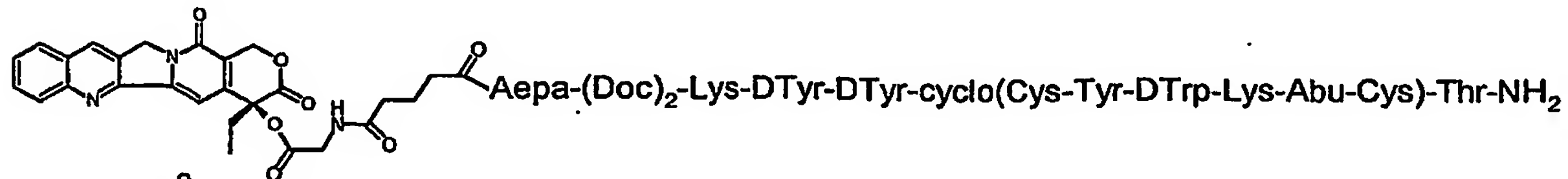
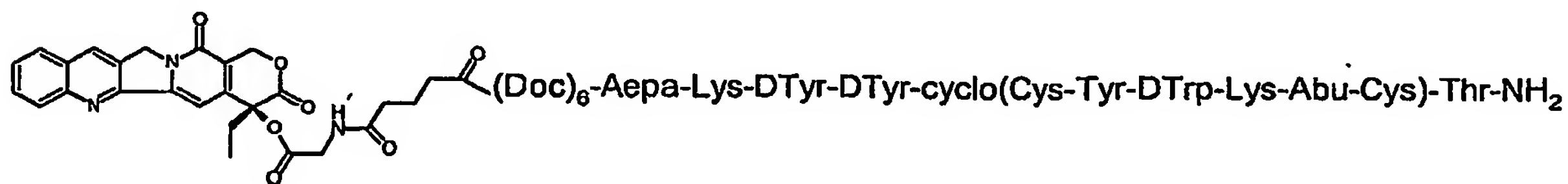
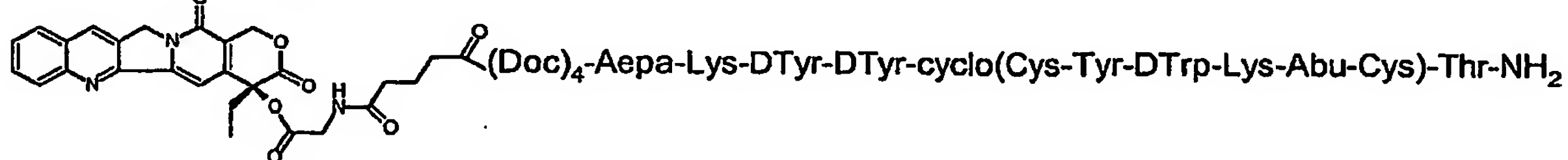
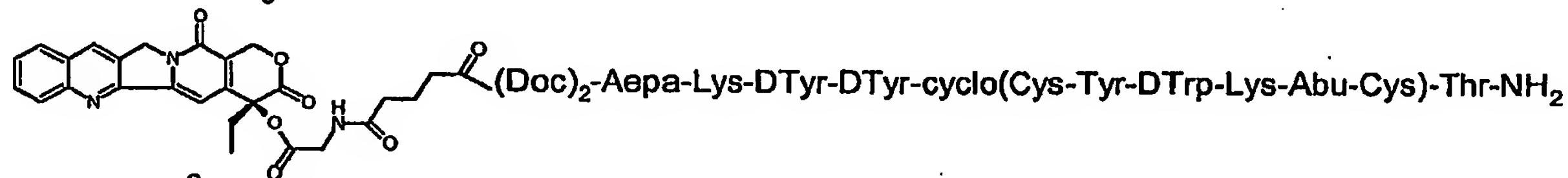
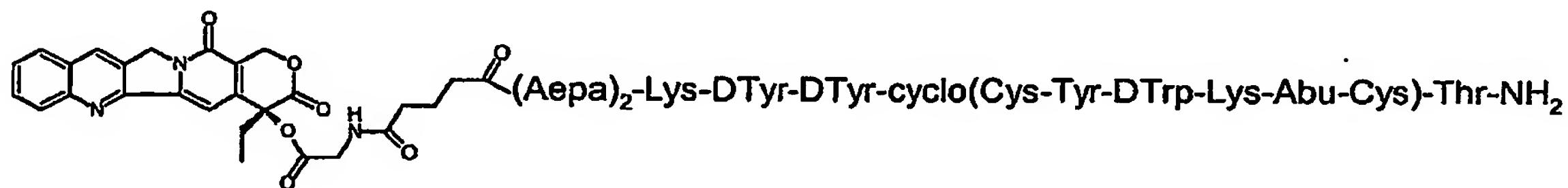
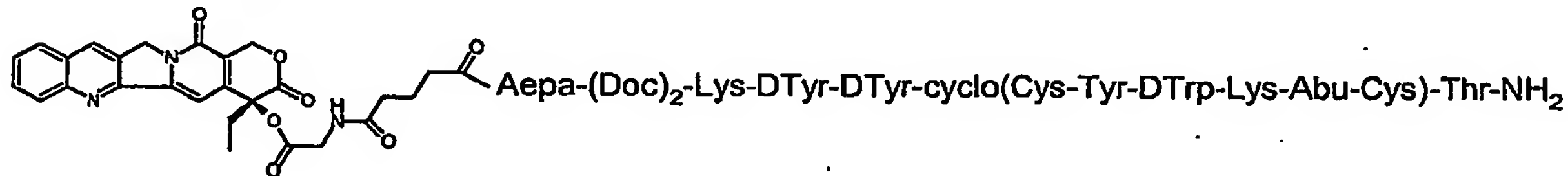
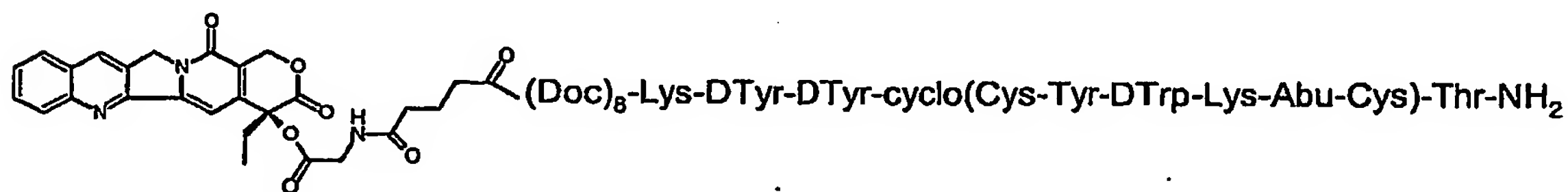
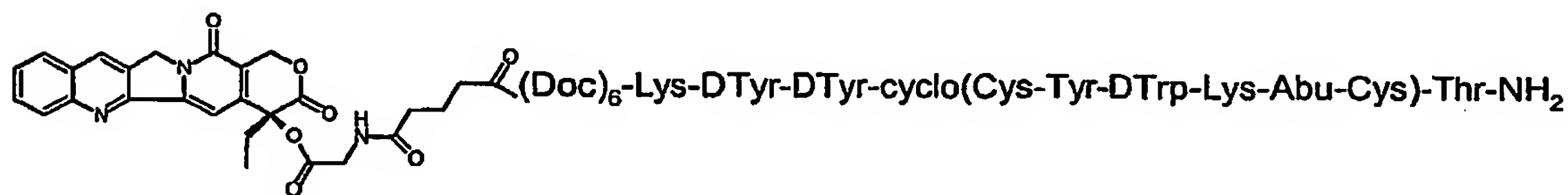
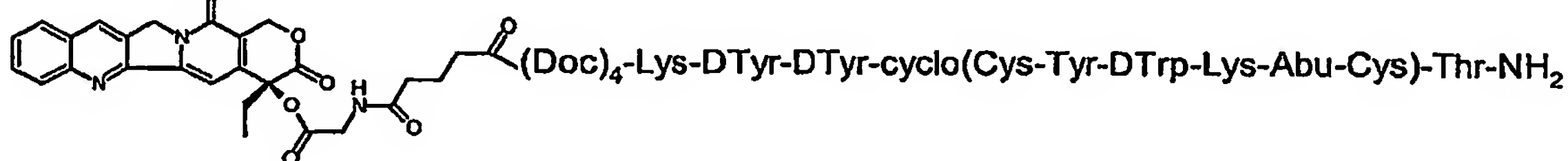
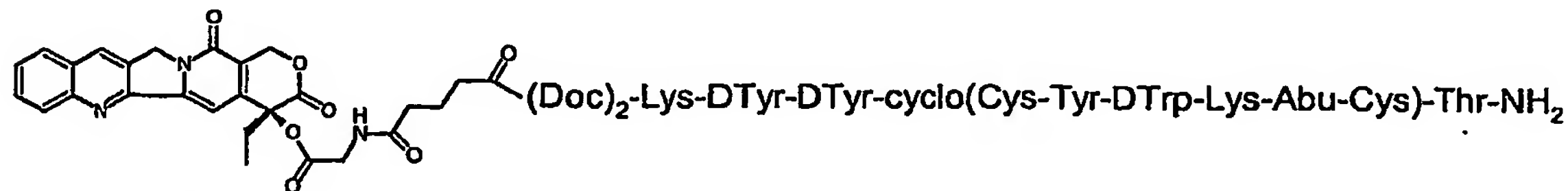
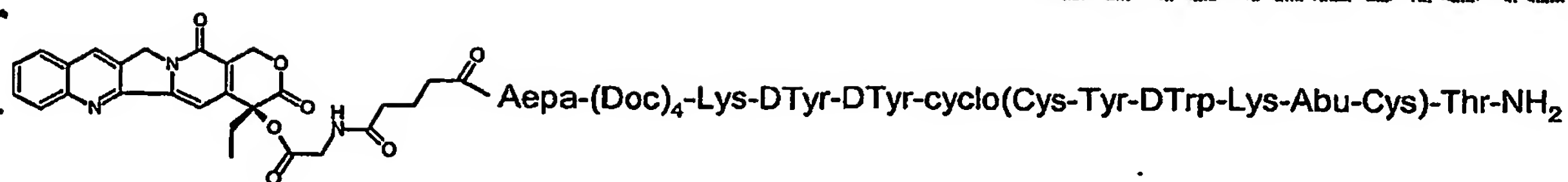












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UNITED STATES DEPARTMENT OF COMMERCE

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February 10, 2004

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APPLICATION NUMBER: 60/464,528

FILING DATE: April 22, 2003

**PRIORITY
DOCUMENT**
SUBMITTED OR TRANSMITTED IN
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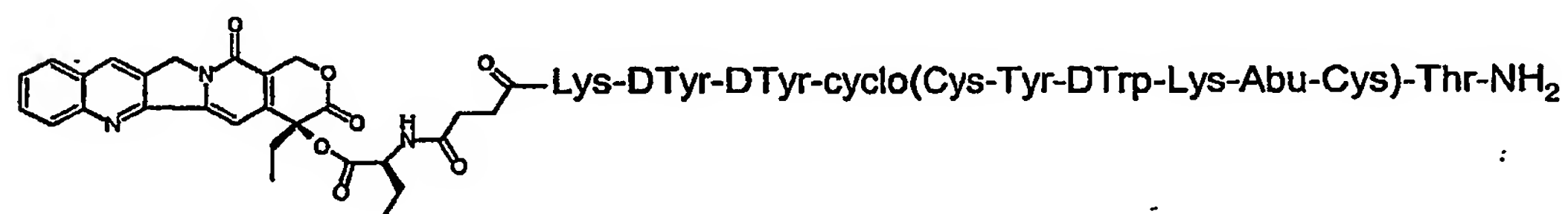
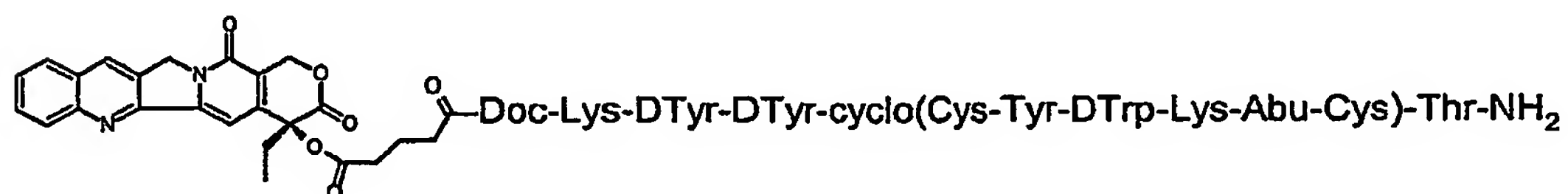
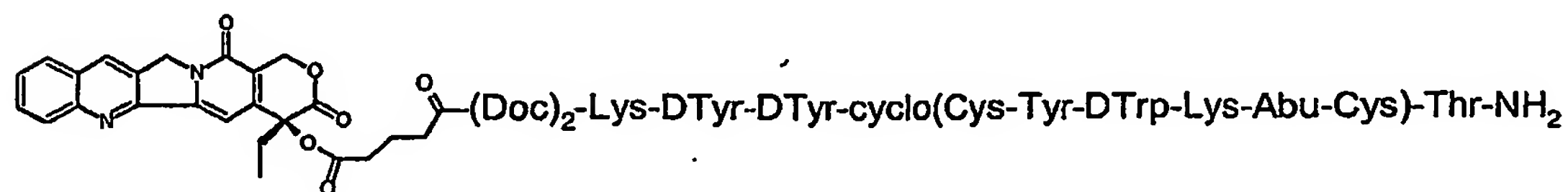
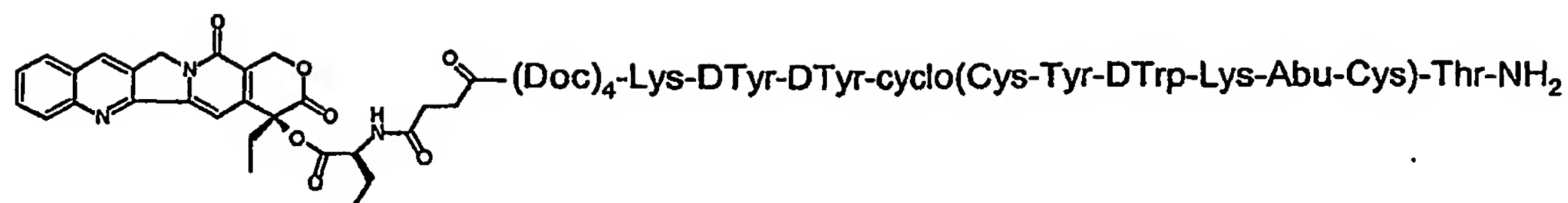


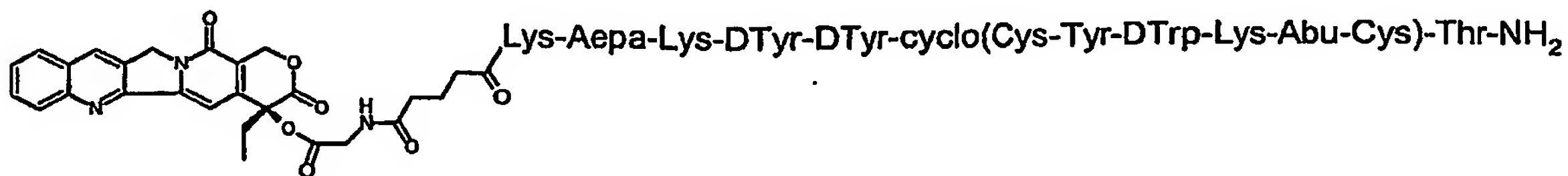
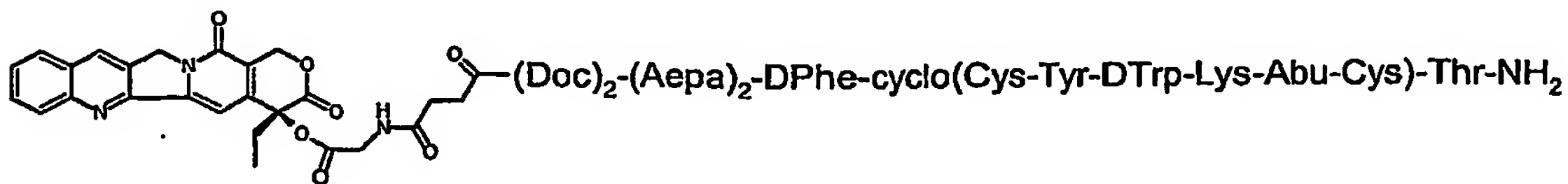
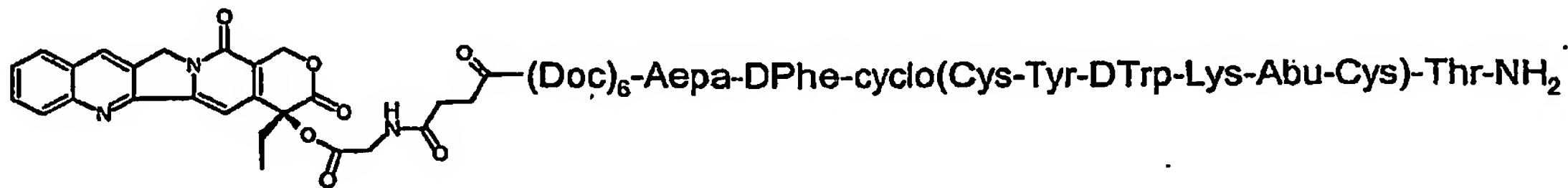
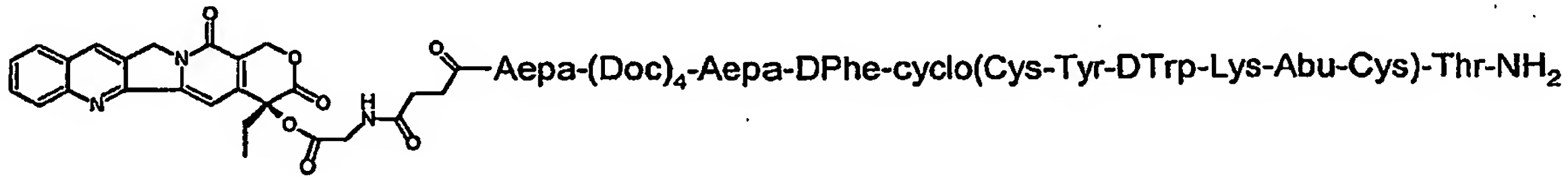
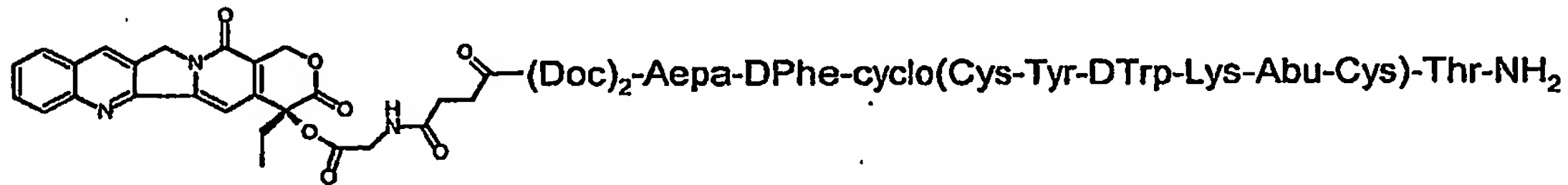
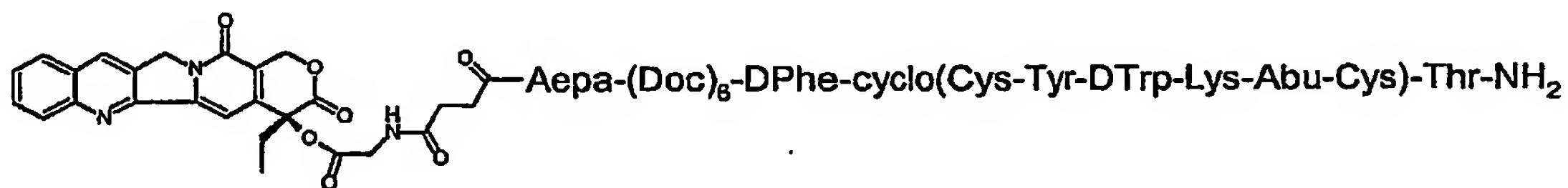
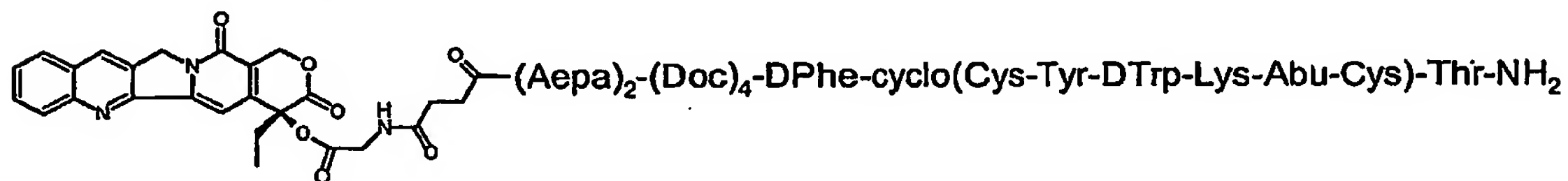
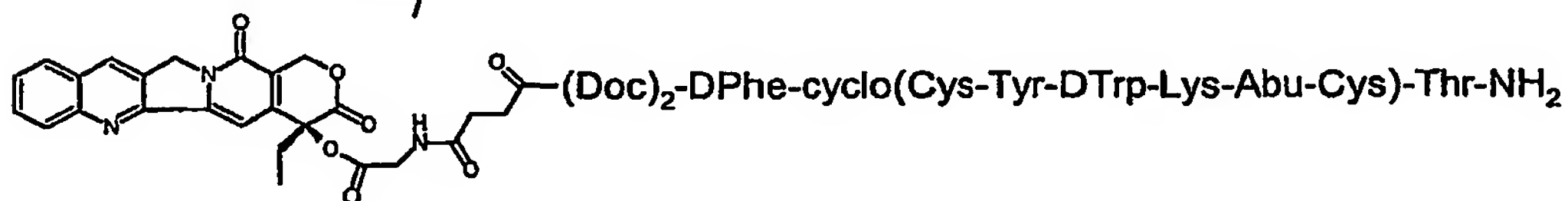
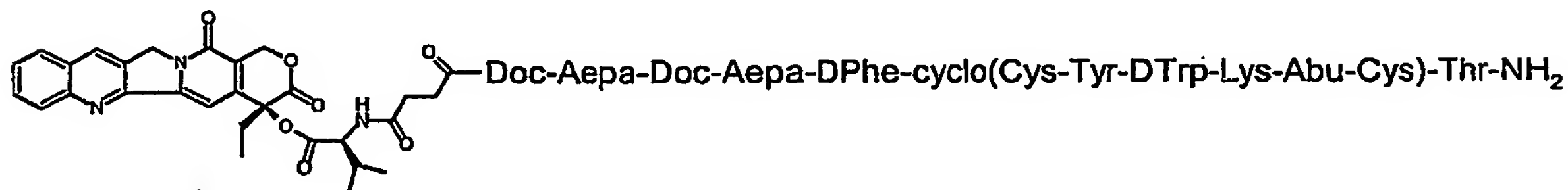
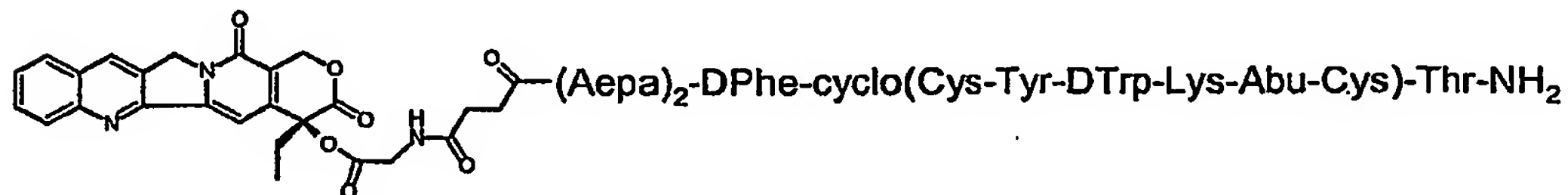
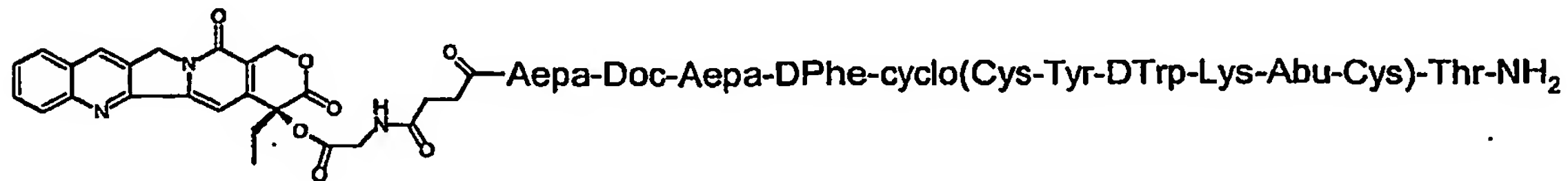
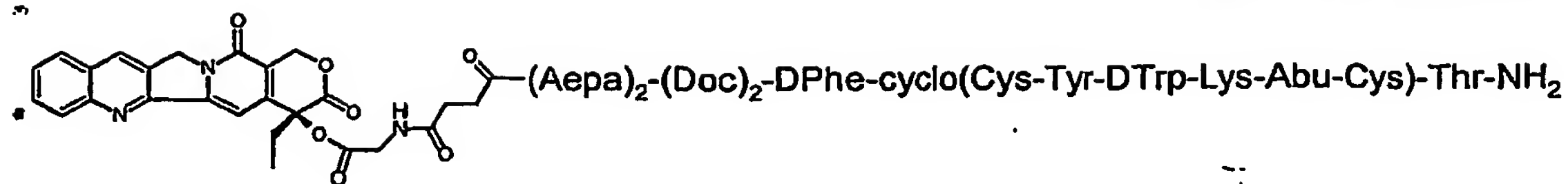
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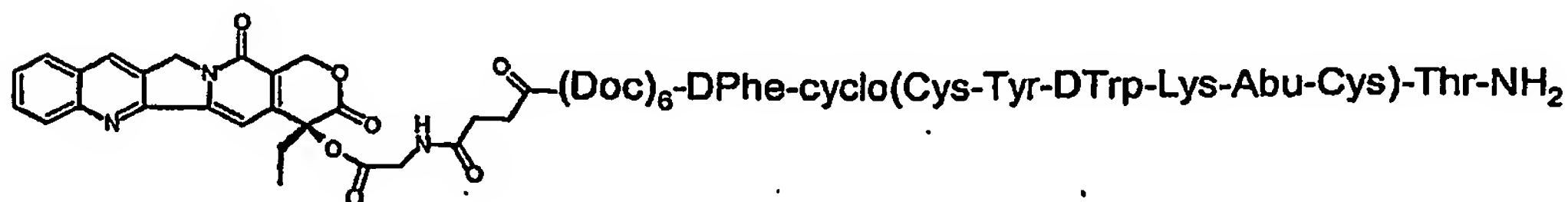
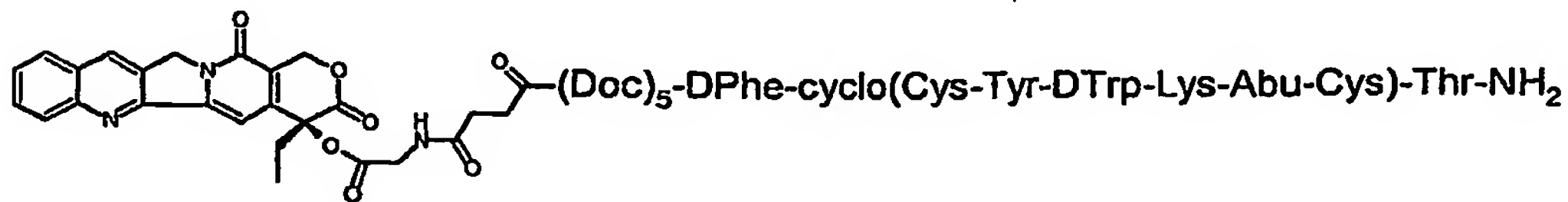
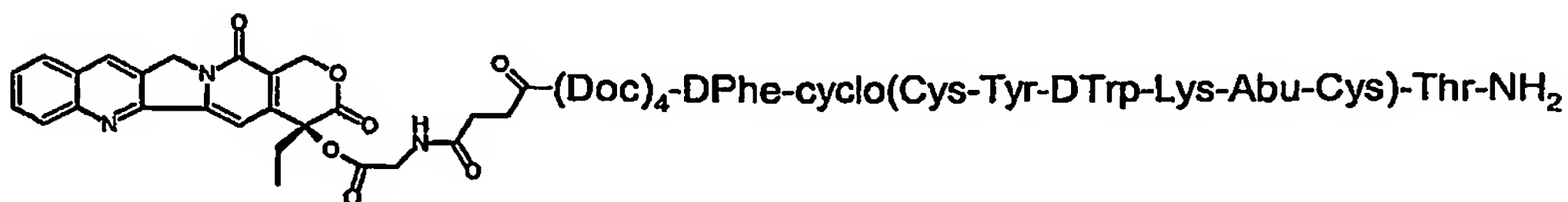
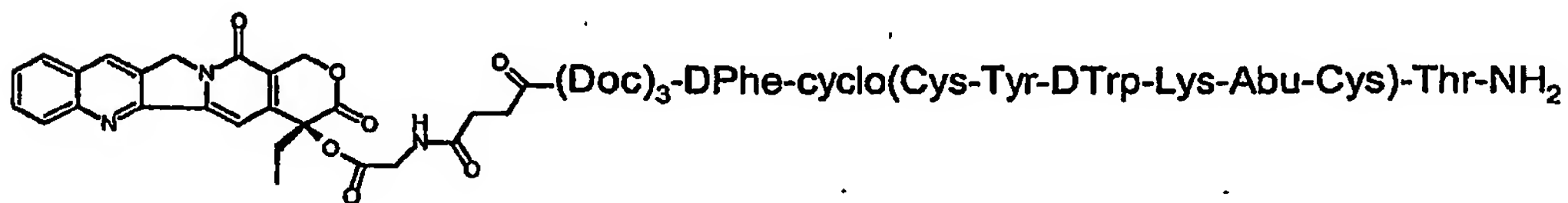
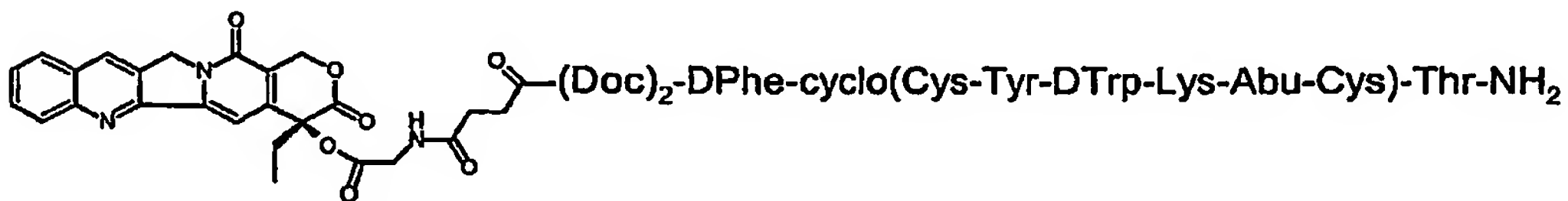
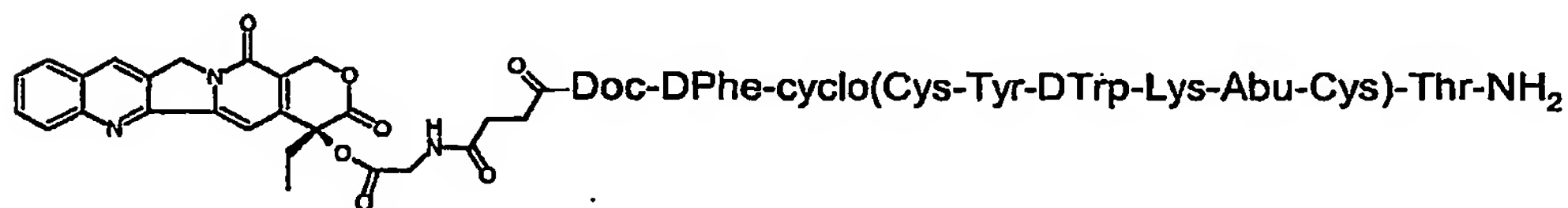
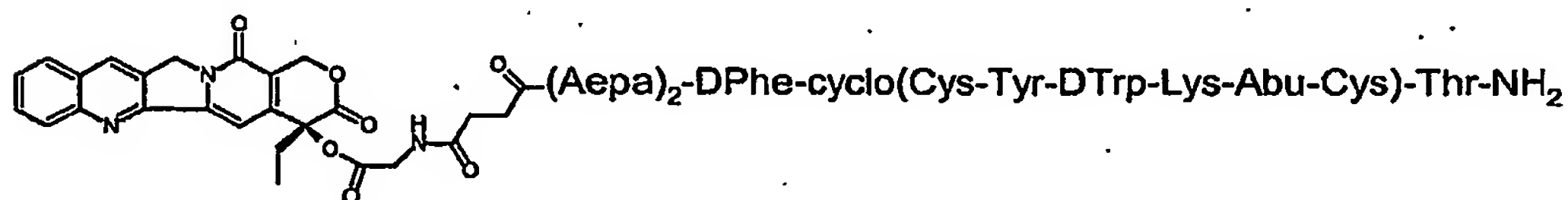
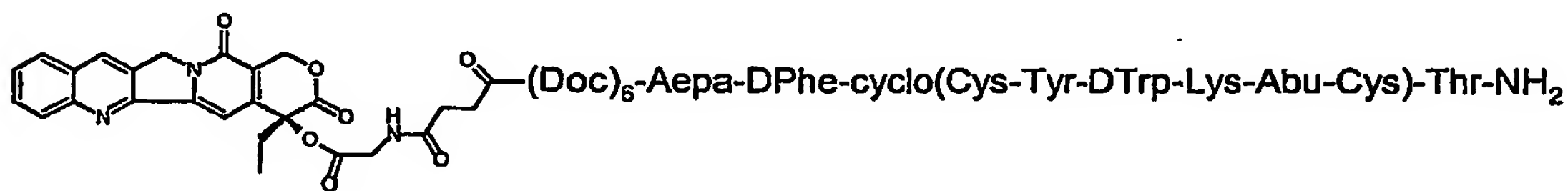
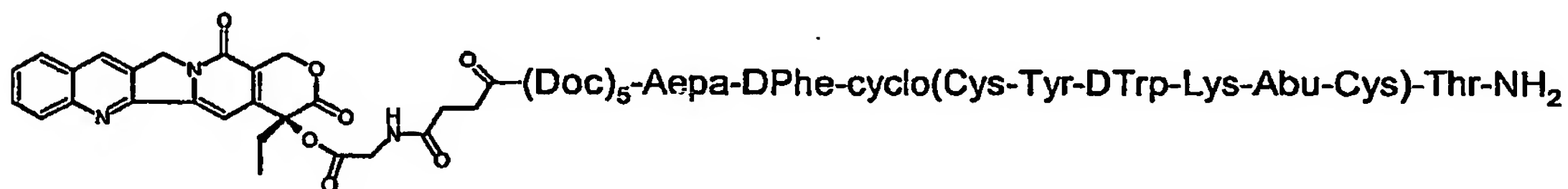
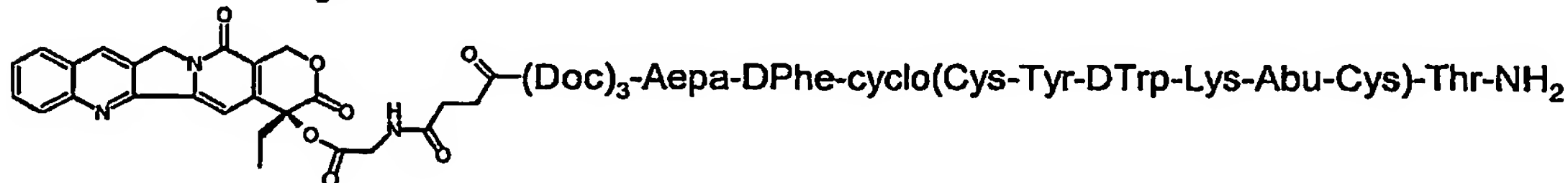
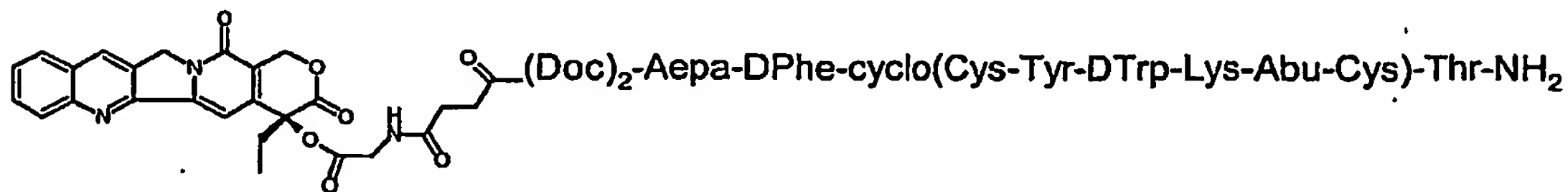
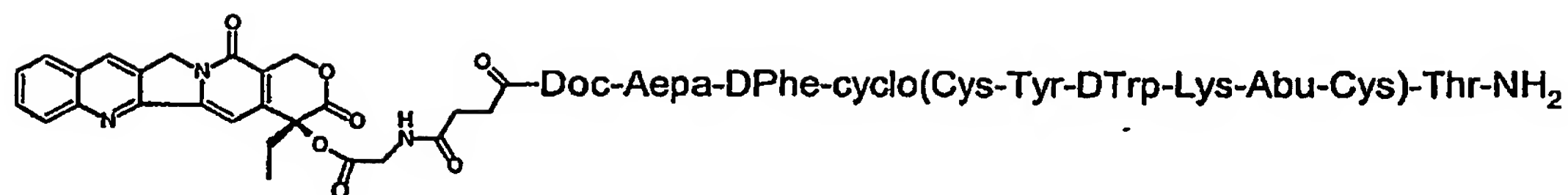

M. K. HAWKINS

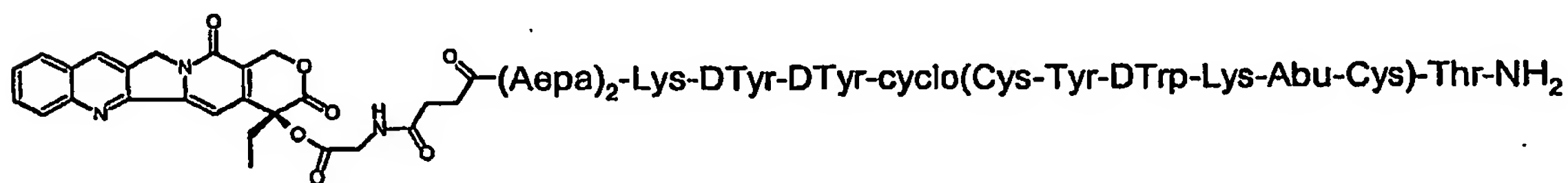
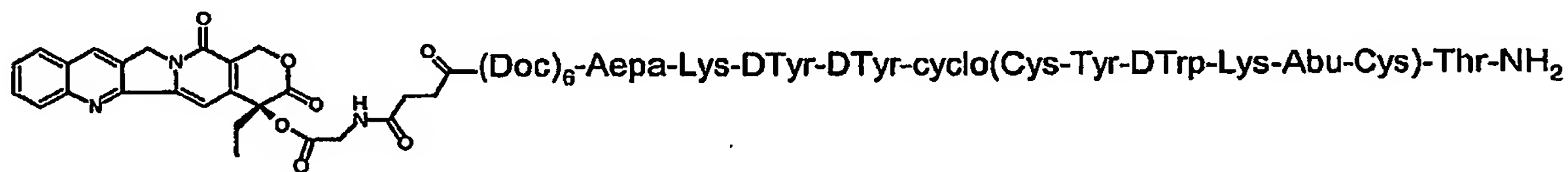
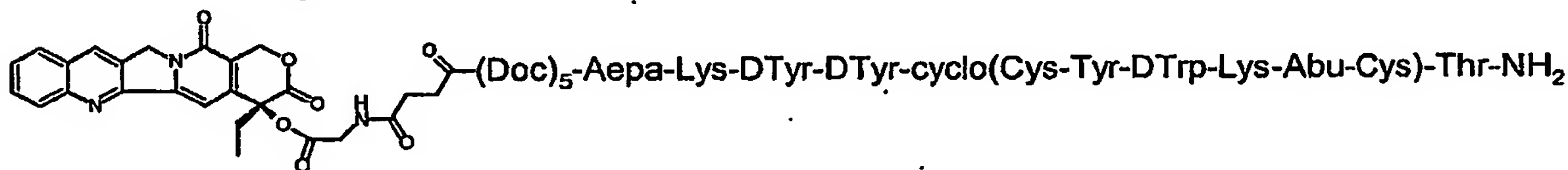
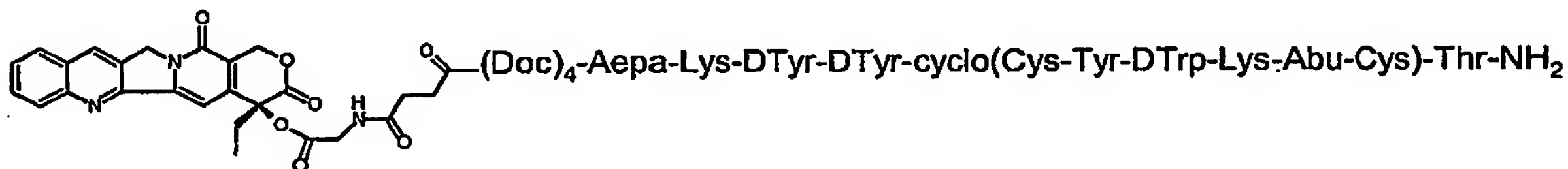
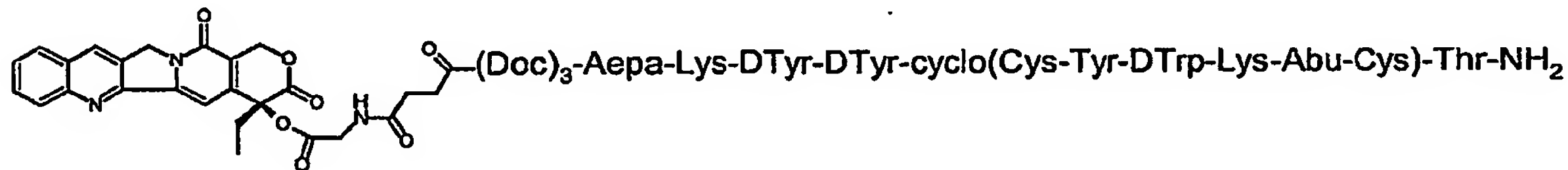
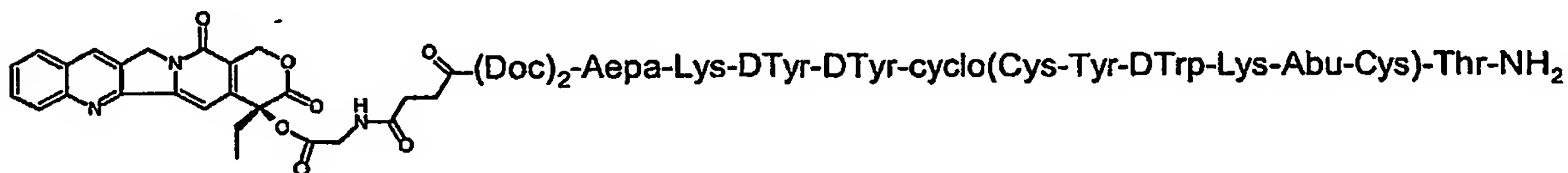
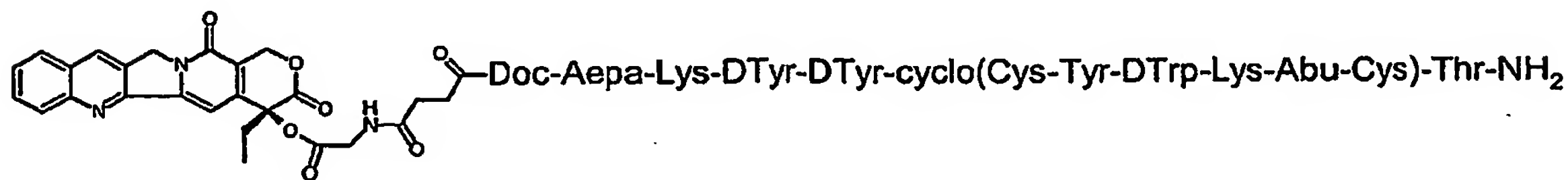
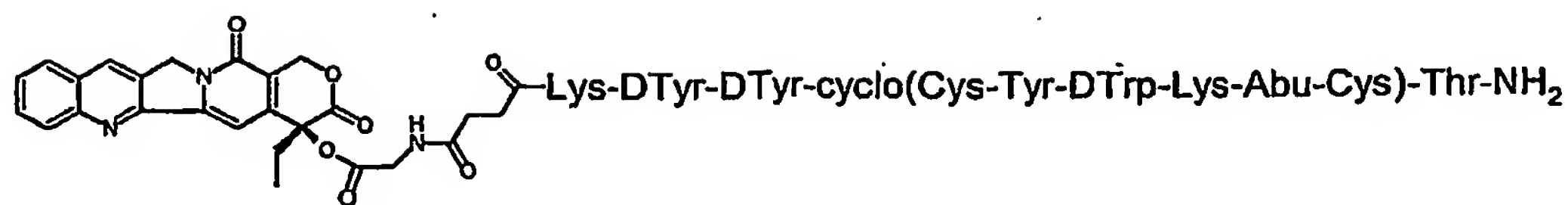
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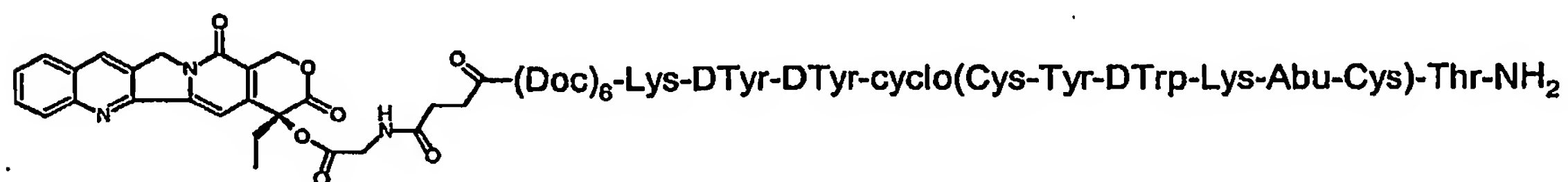
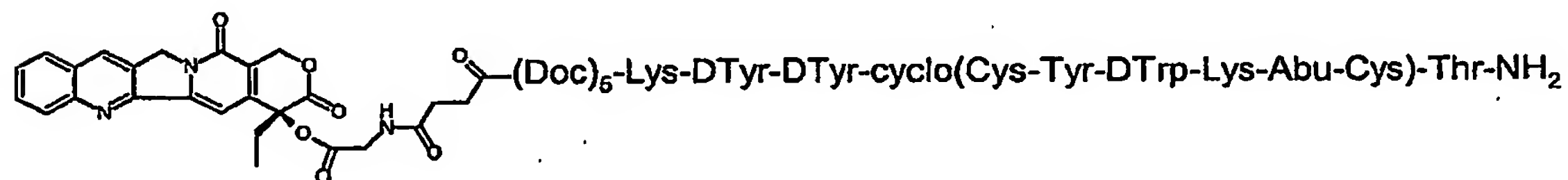
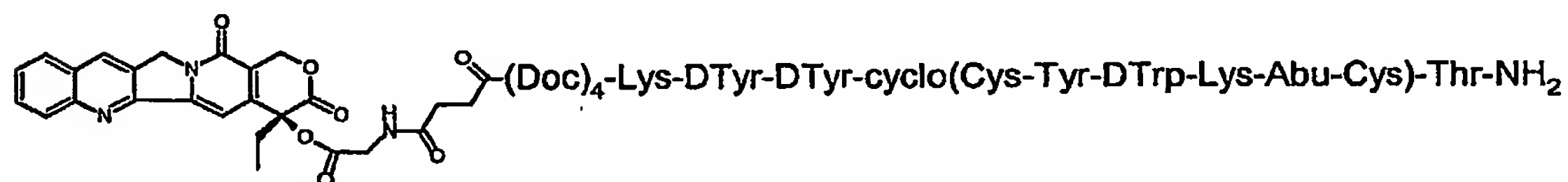
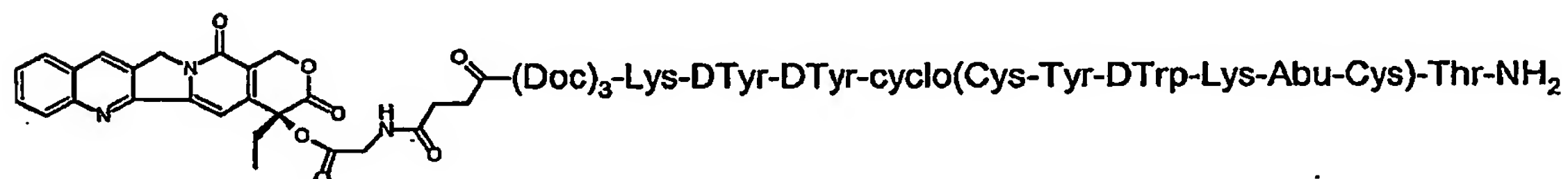
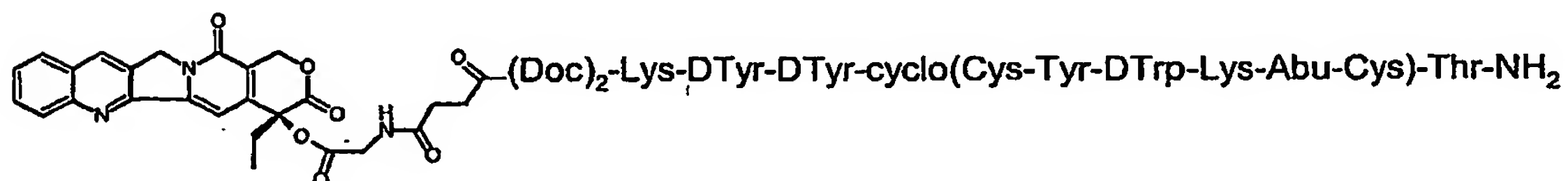
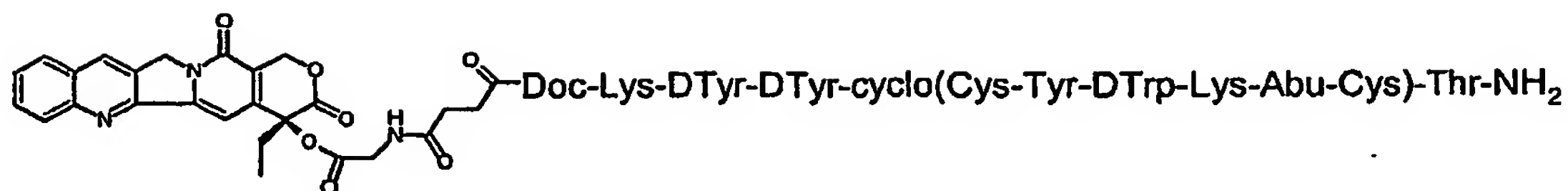
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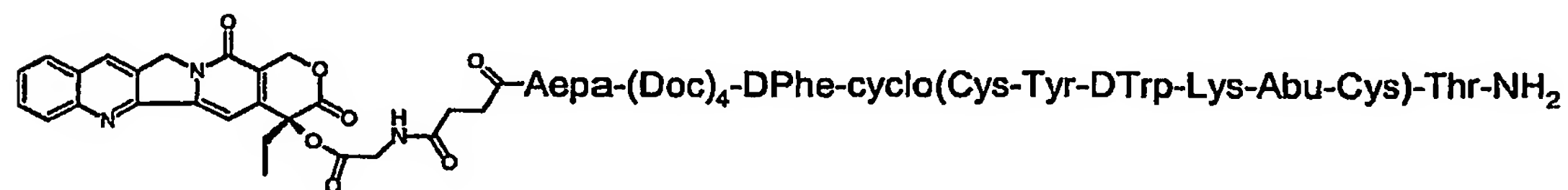
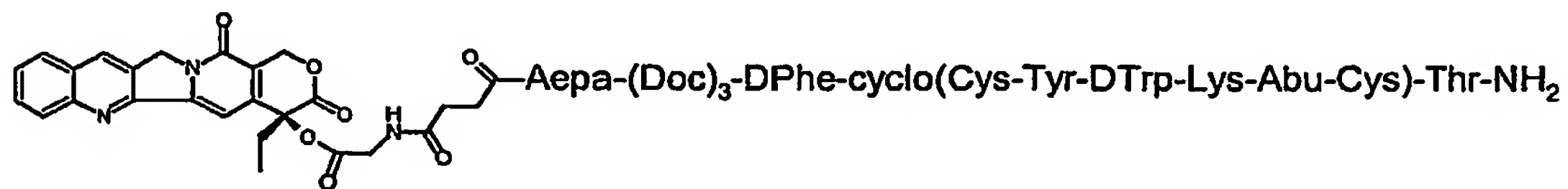
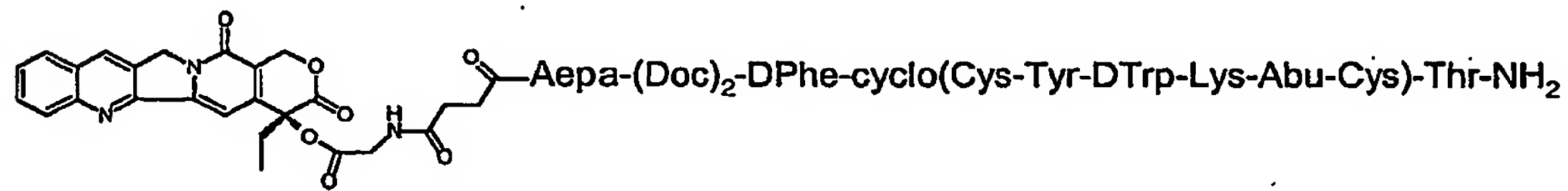
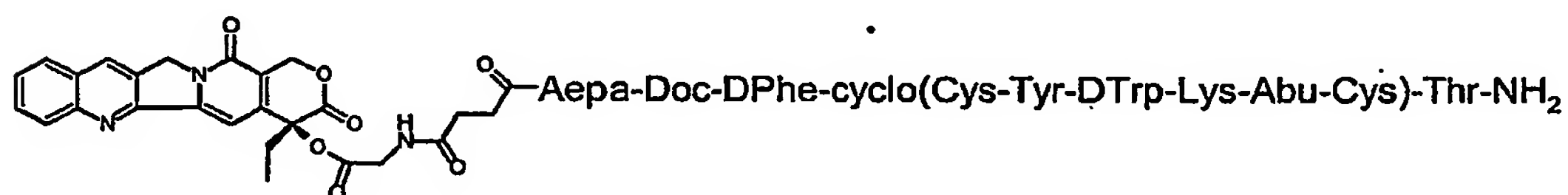
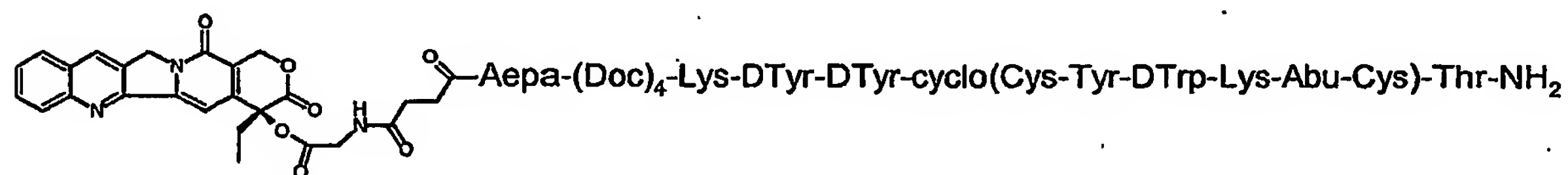
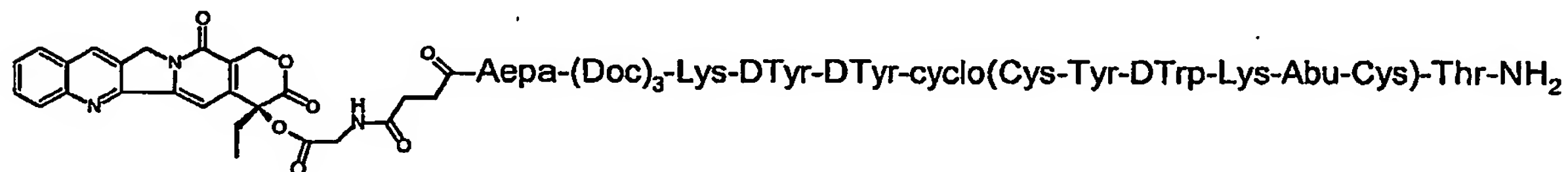
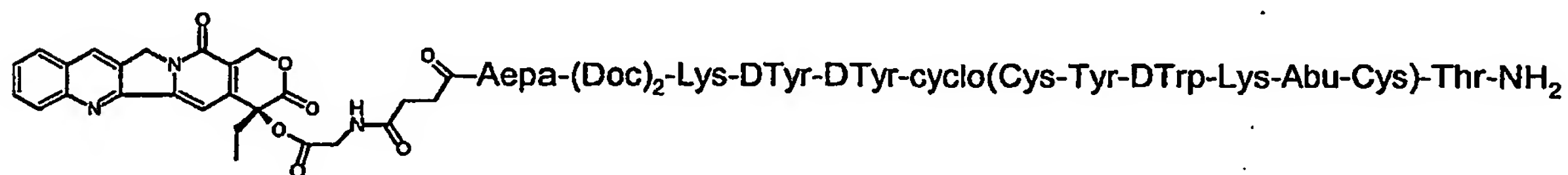
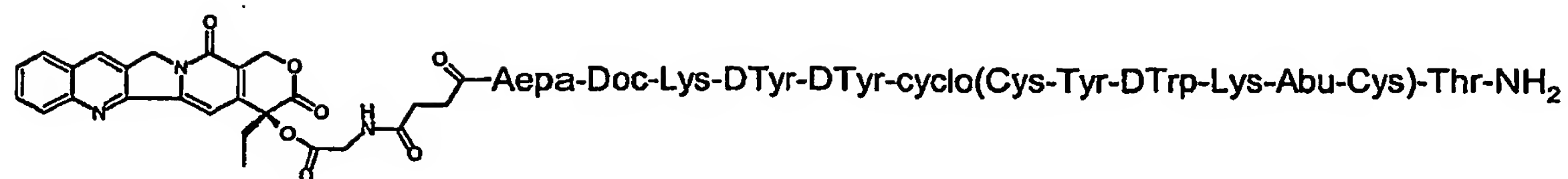




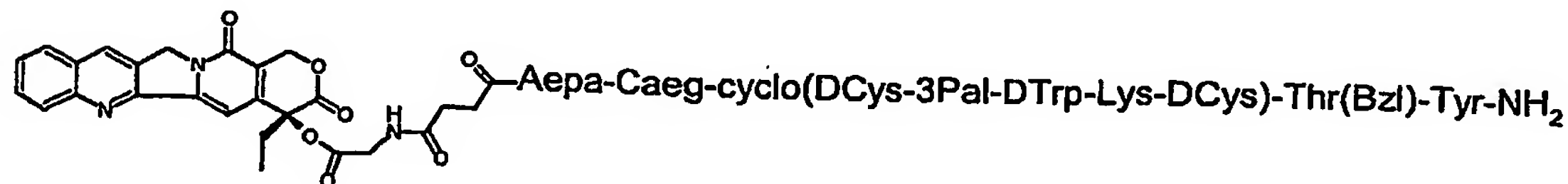
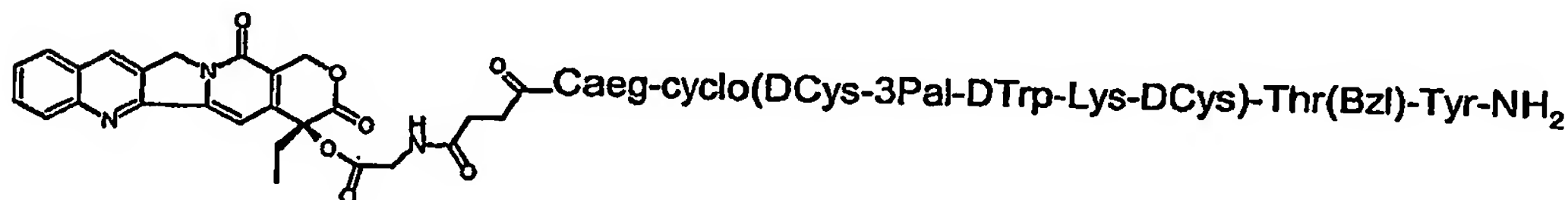
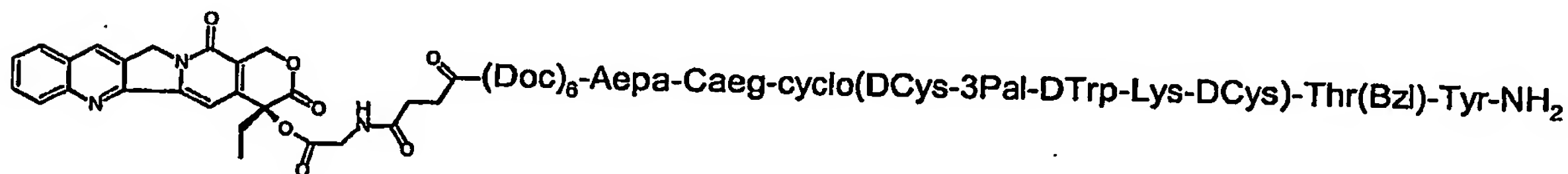
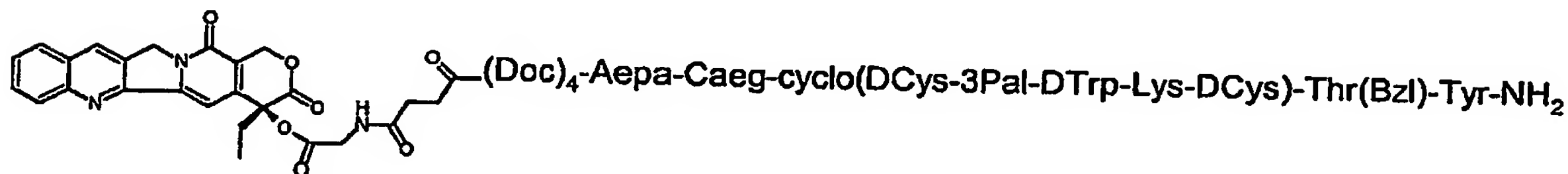
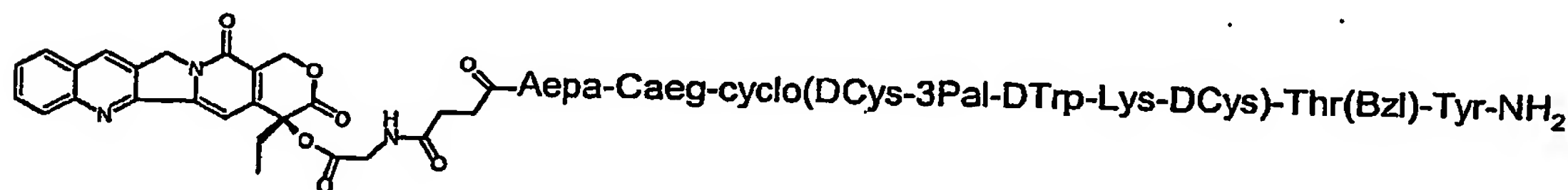
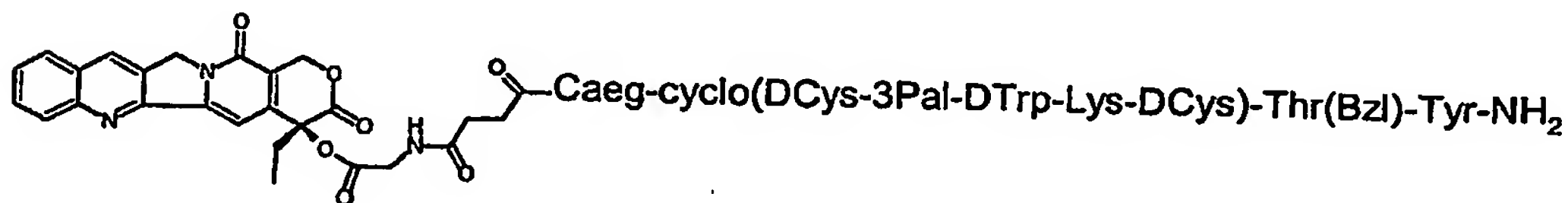
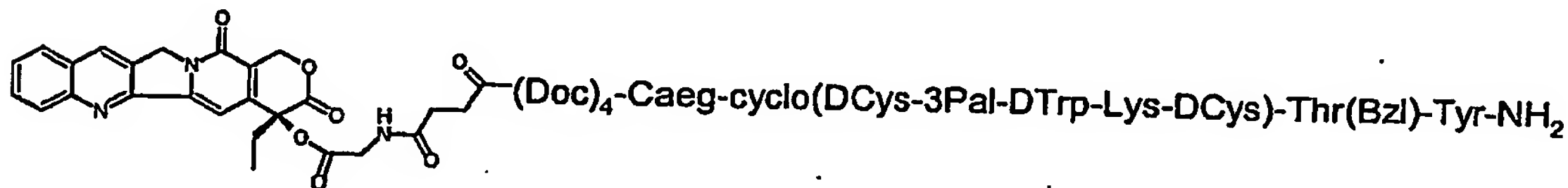
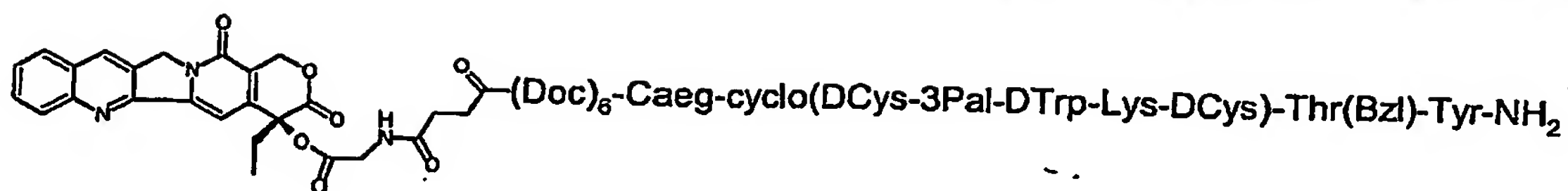


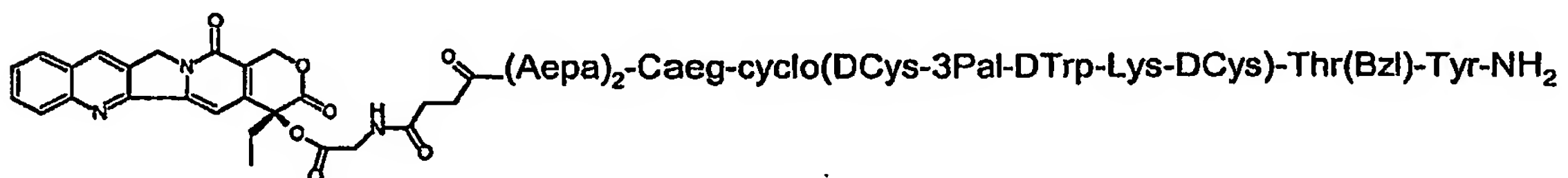
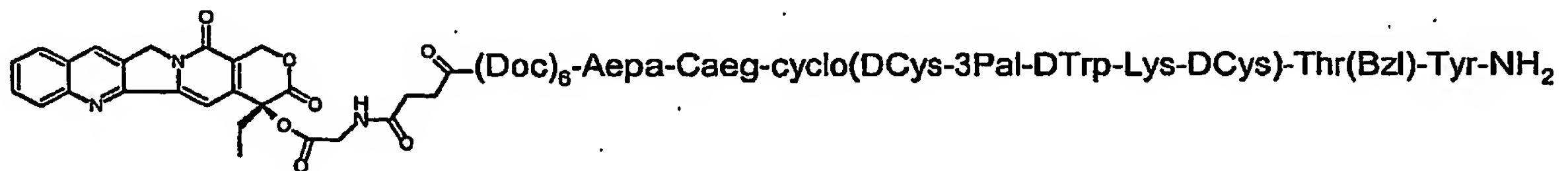
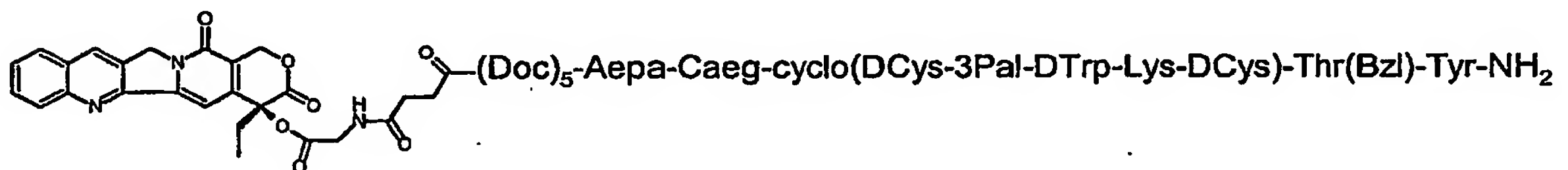
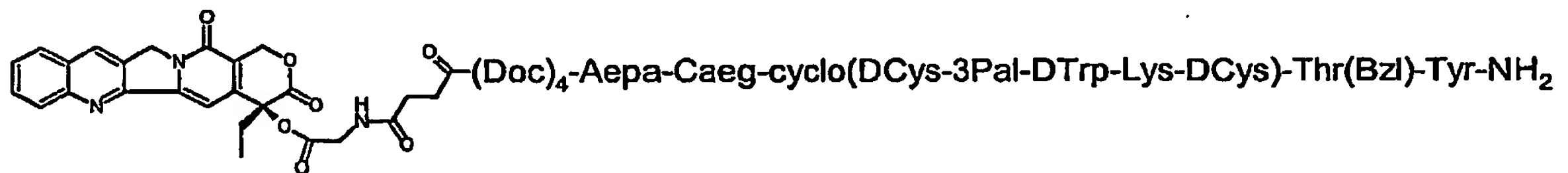
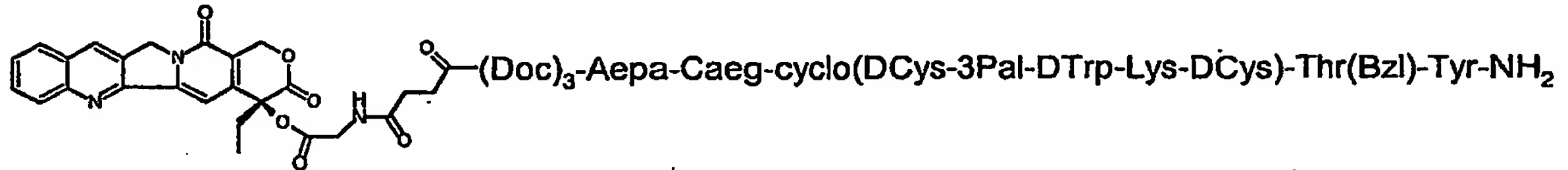
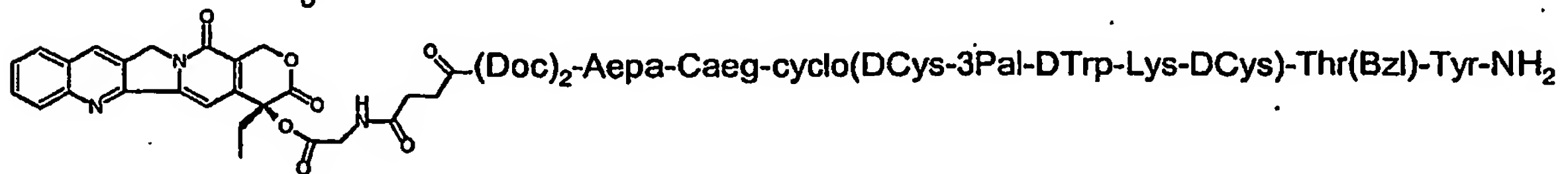
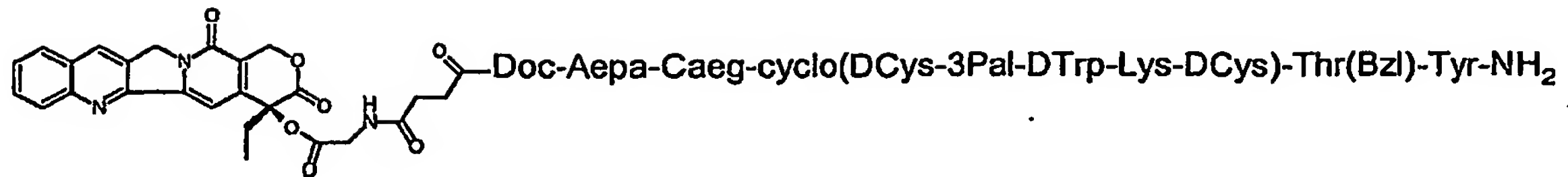


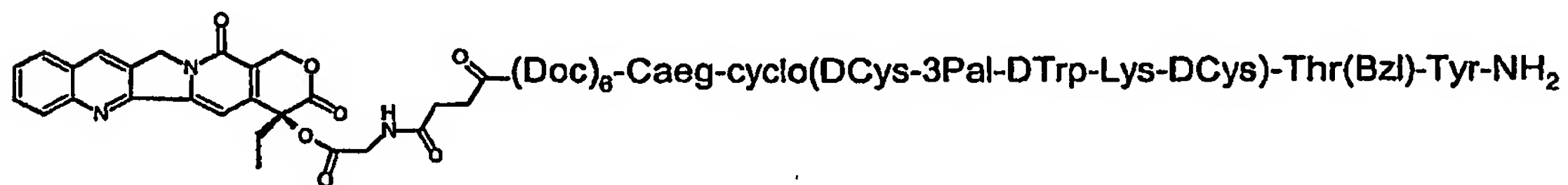
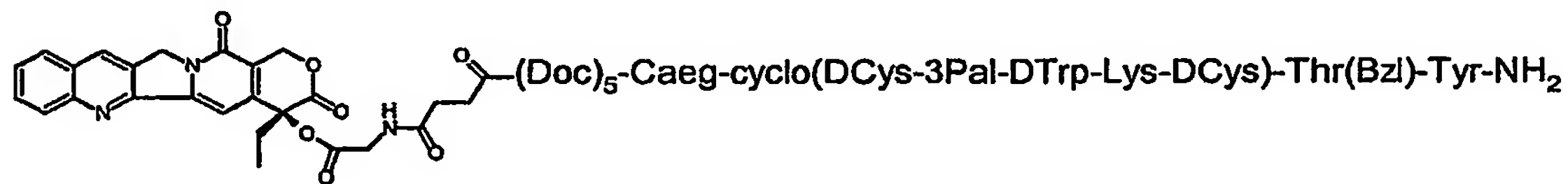
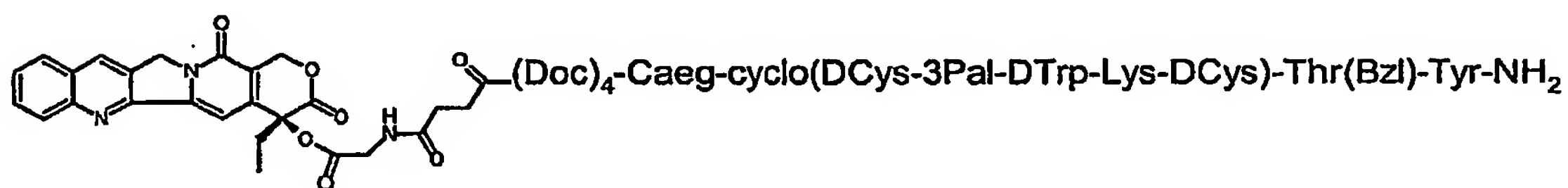
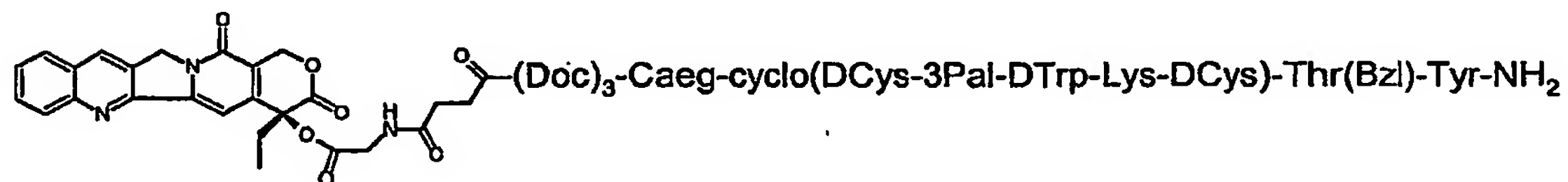
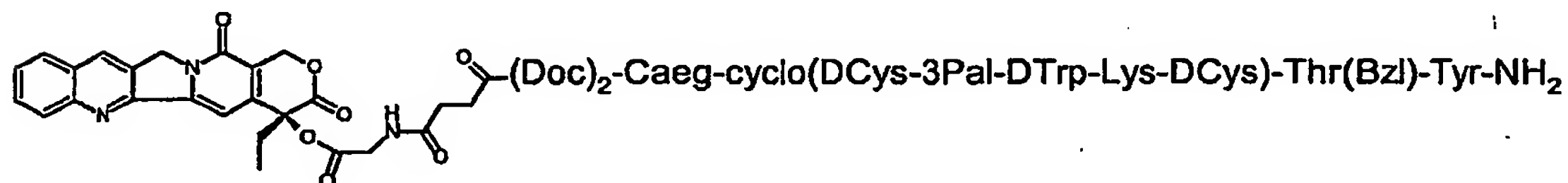
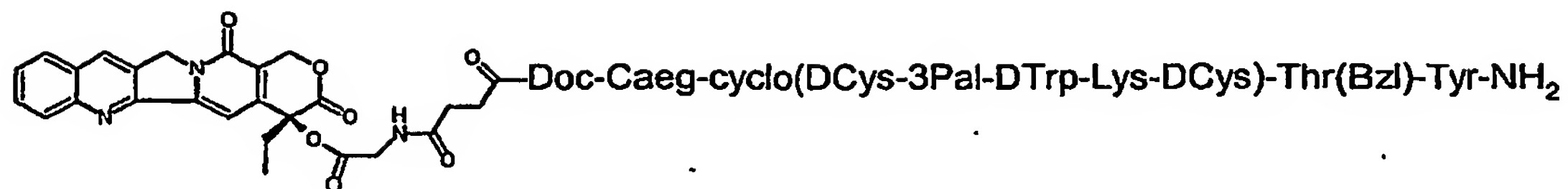
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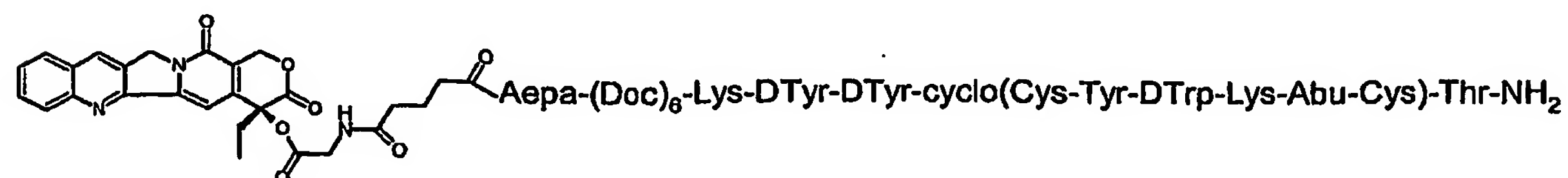
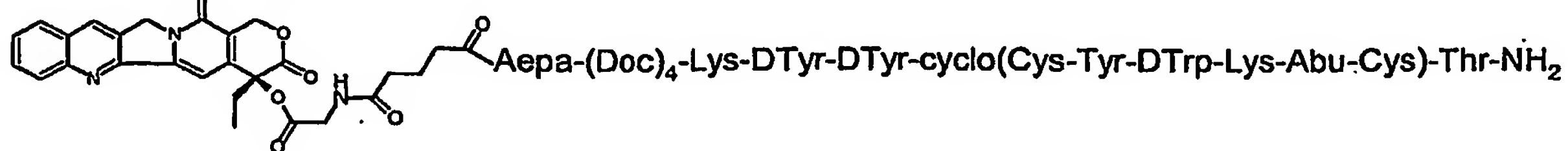
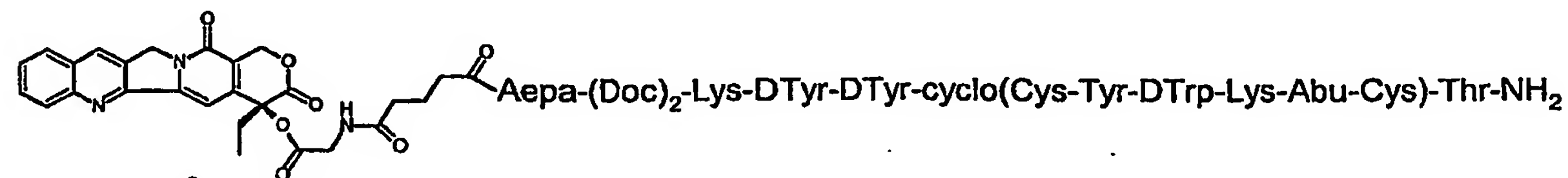
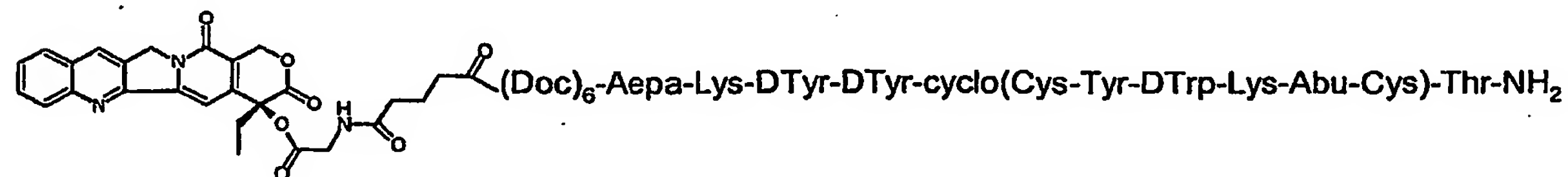
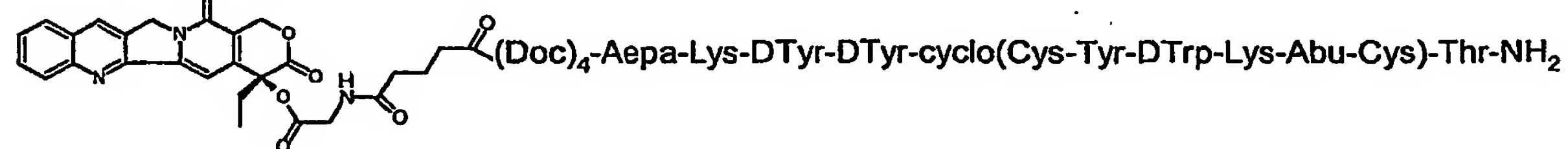
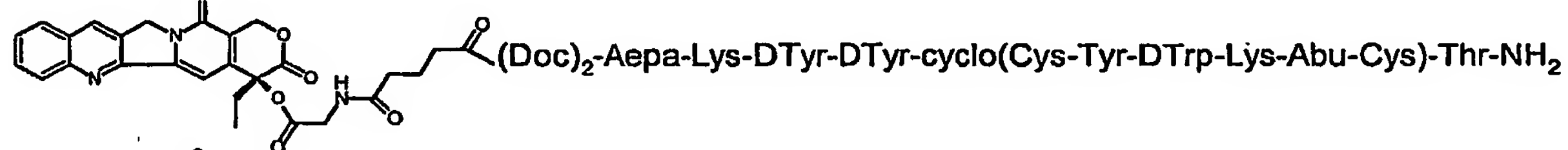
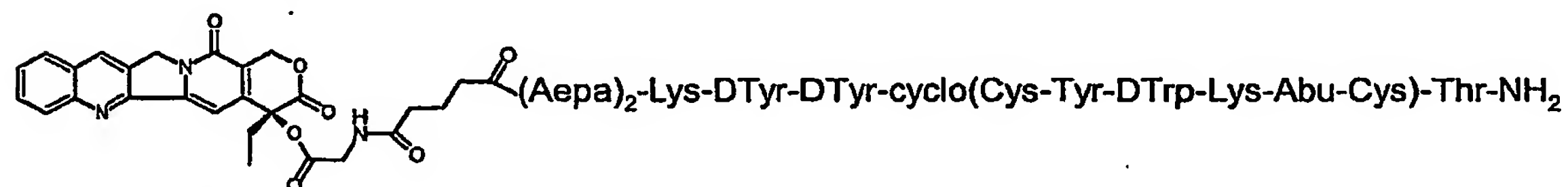
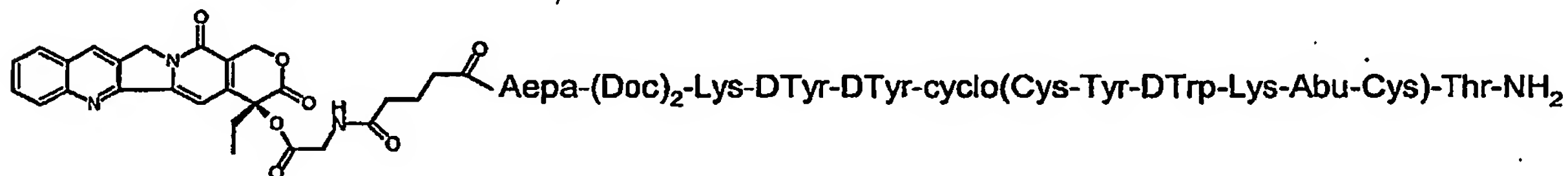
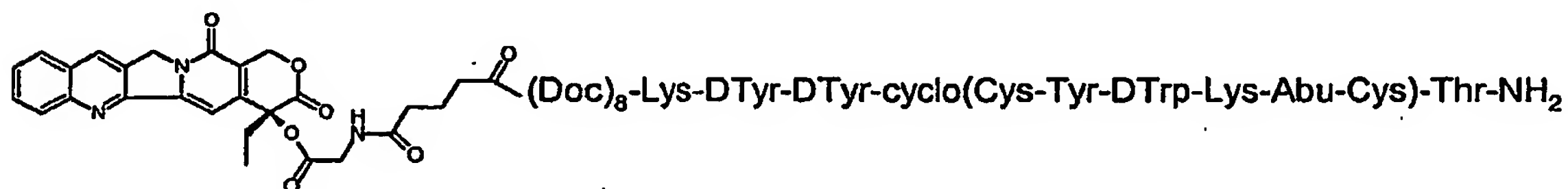
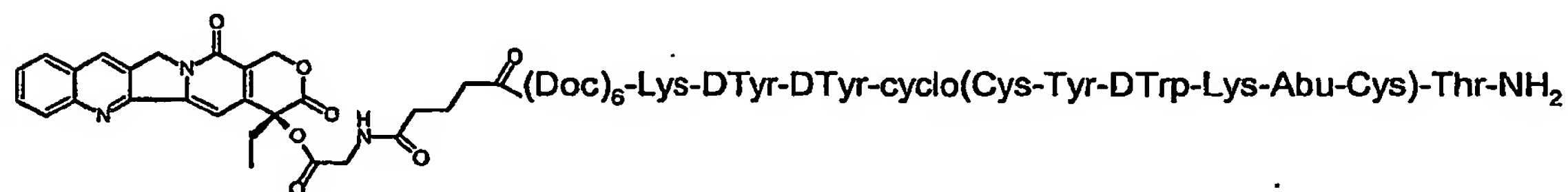
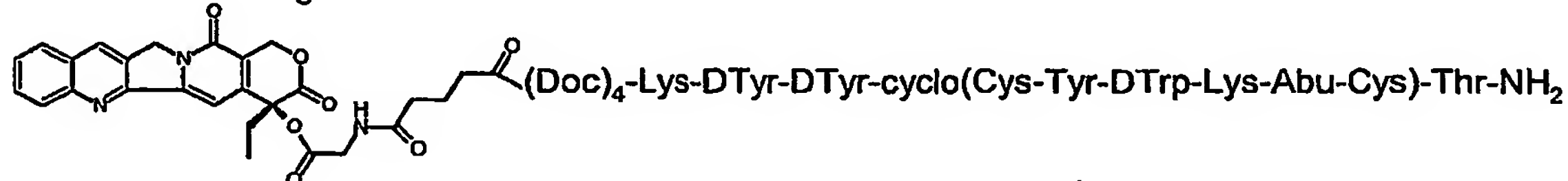
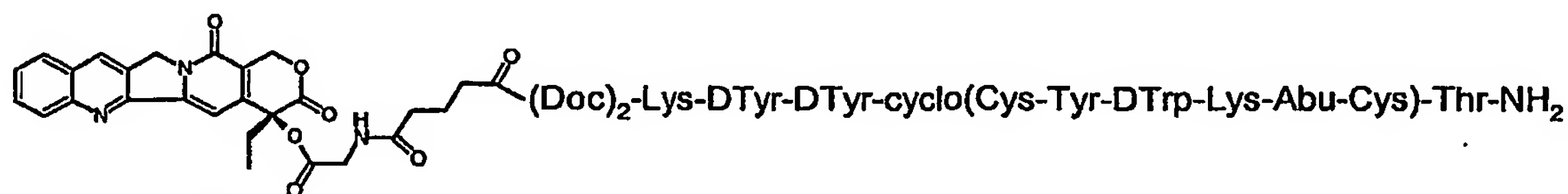
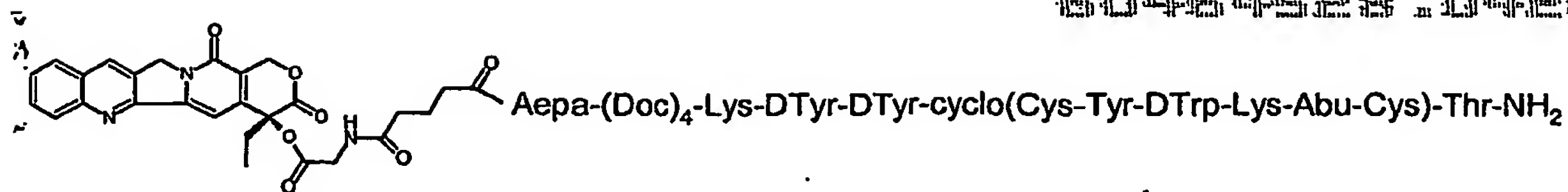


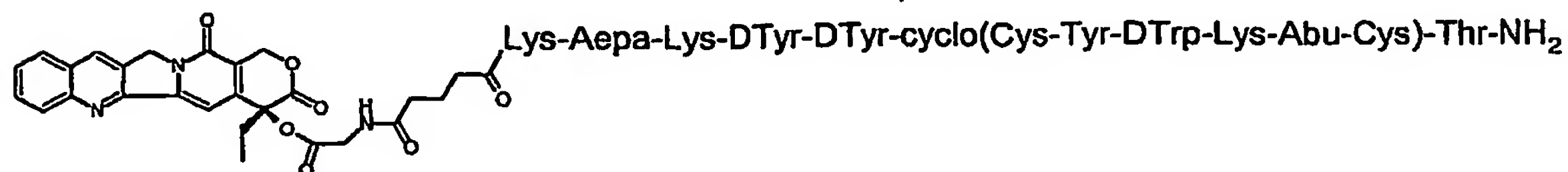
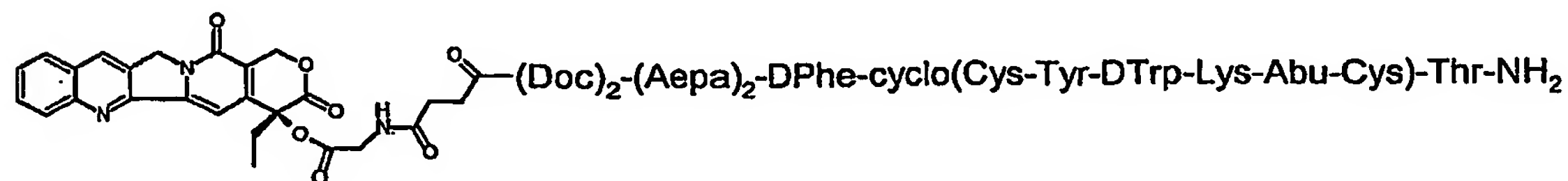
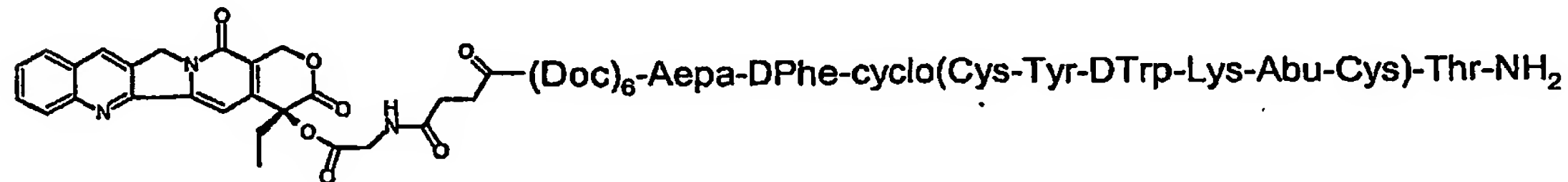
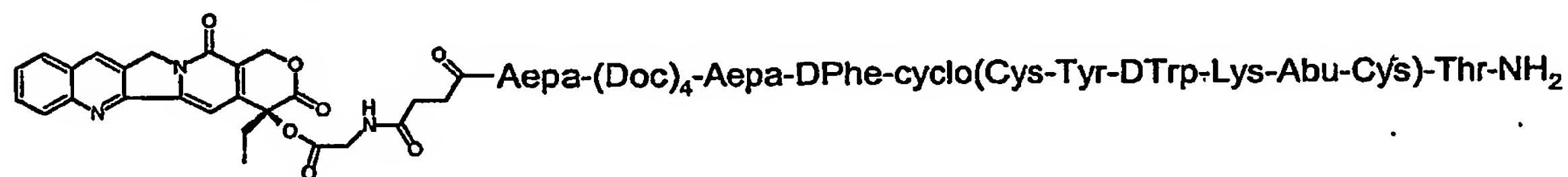
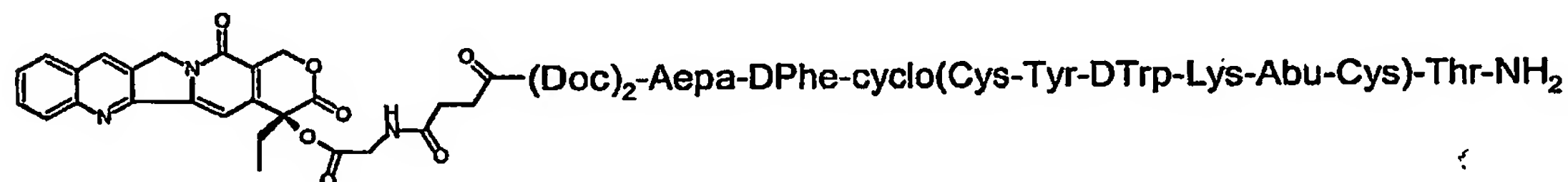
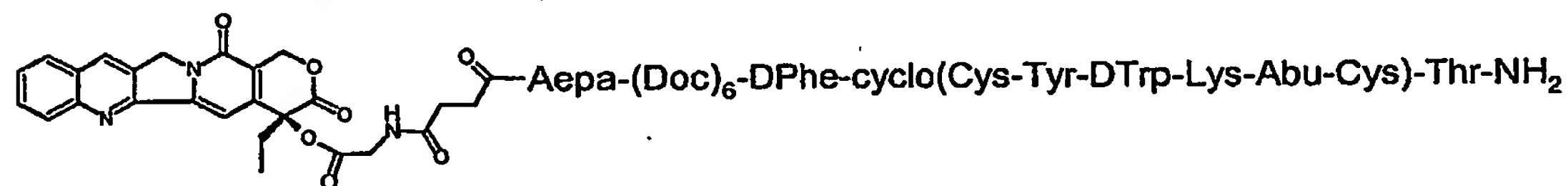
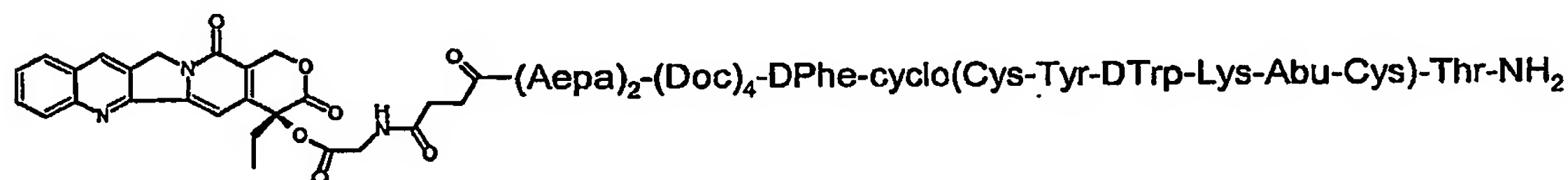
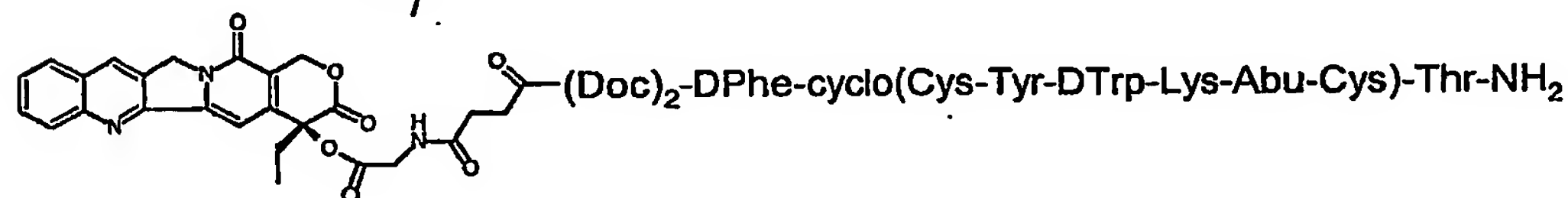
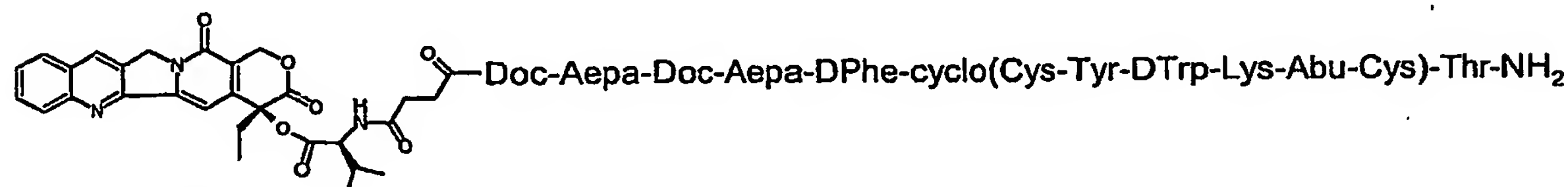
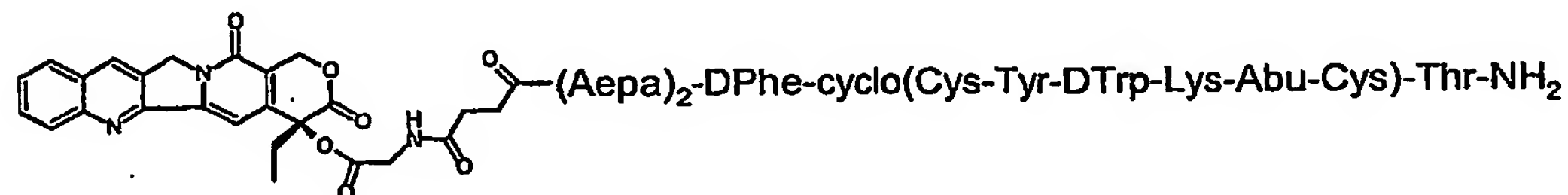
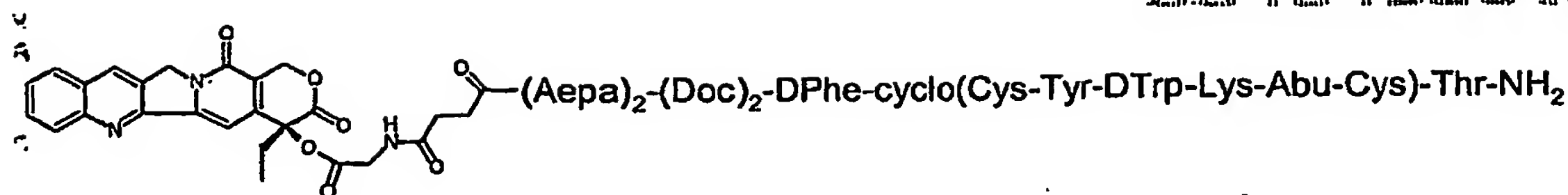
Appendix E

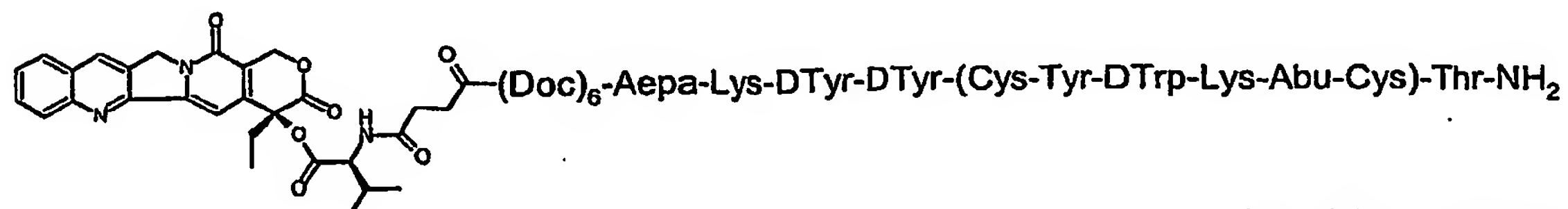
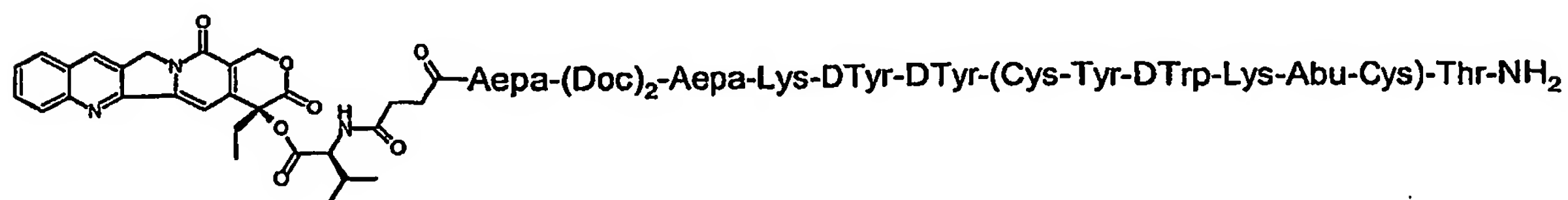
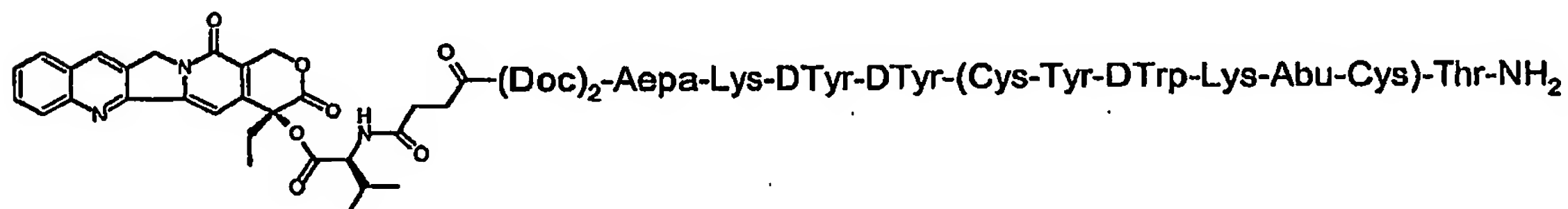
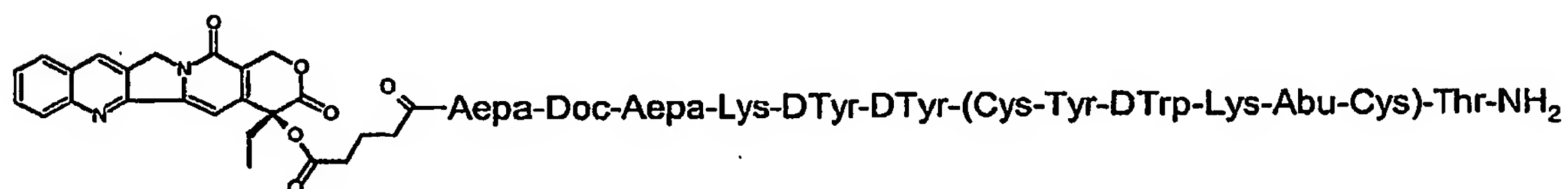
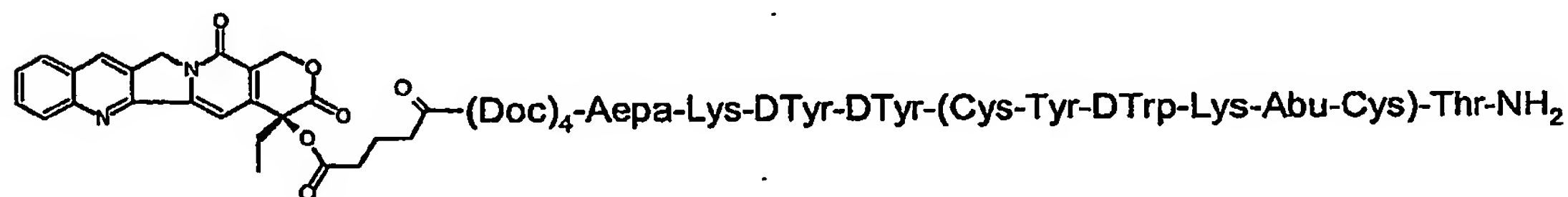
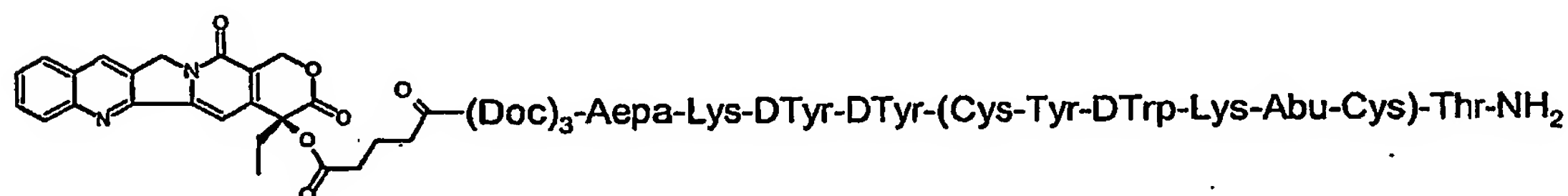
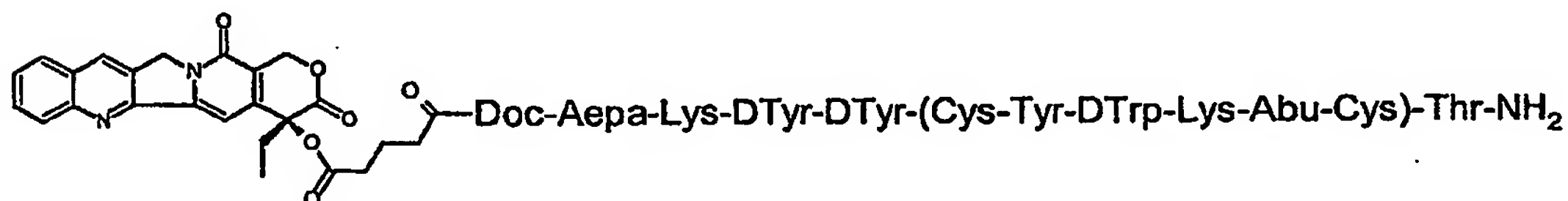
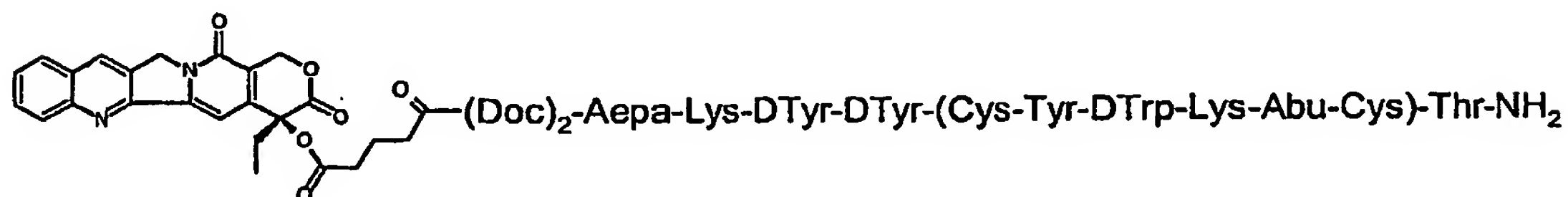
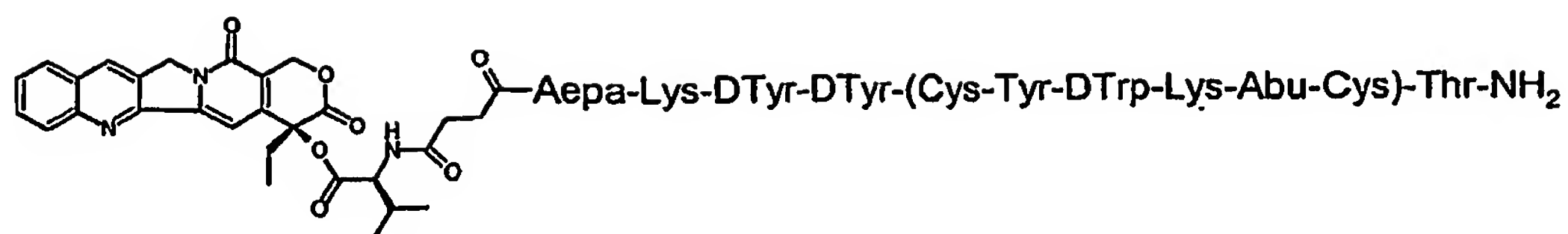


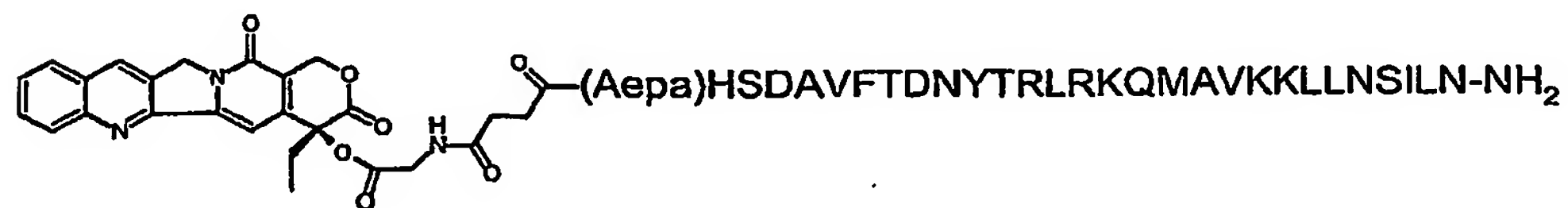
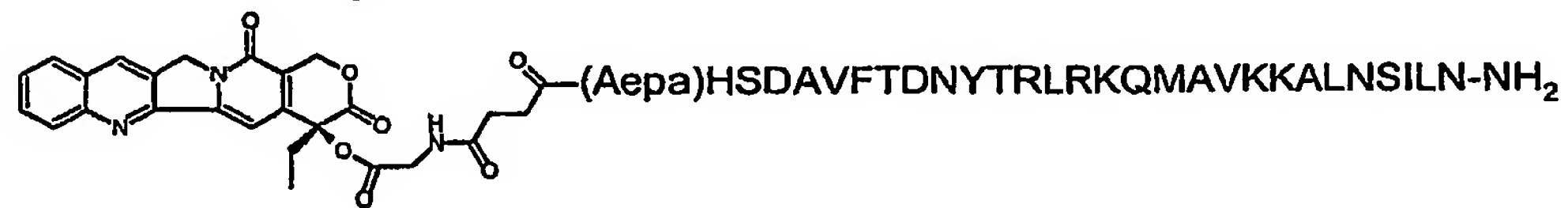
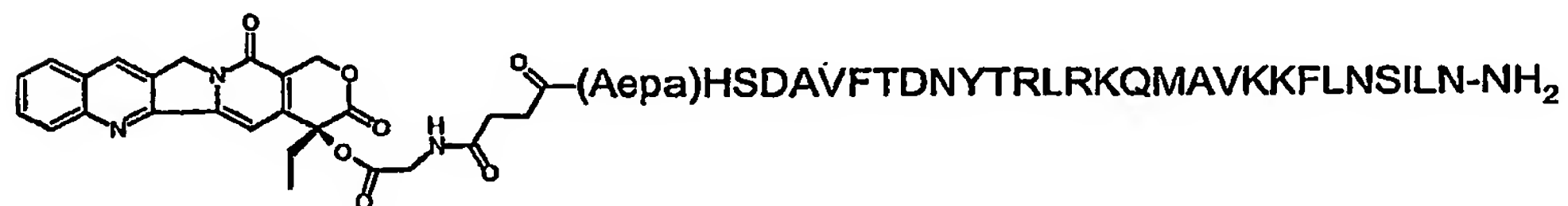
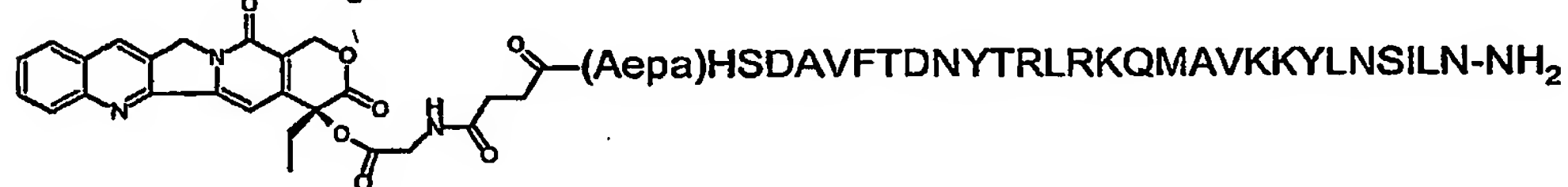
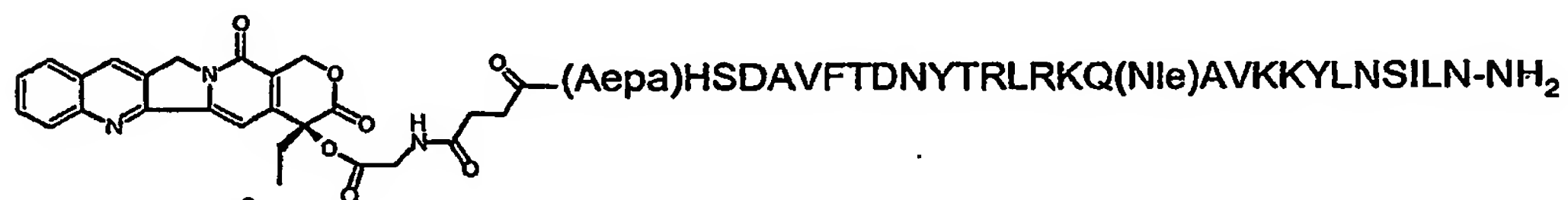
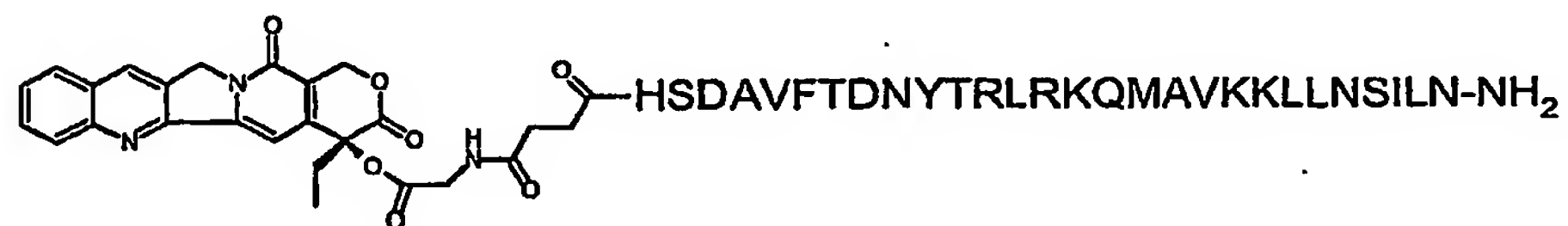
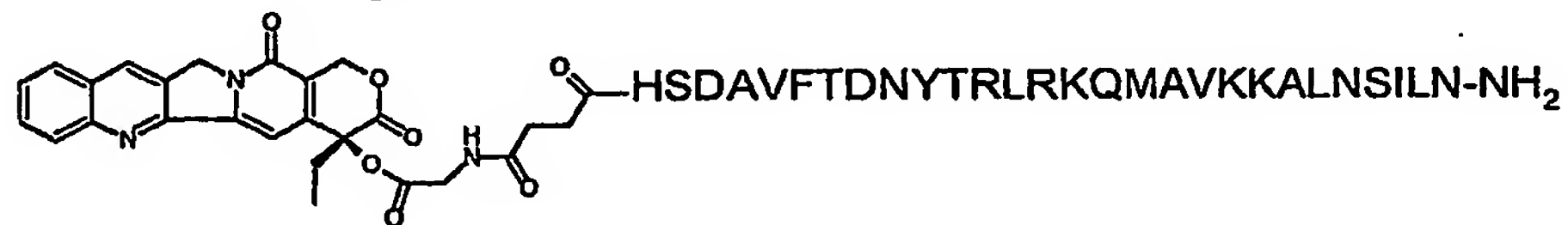


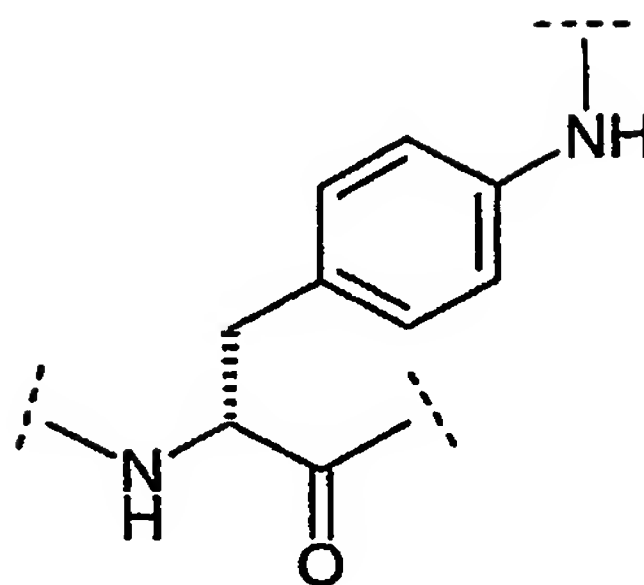
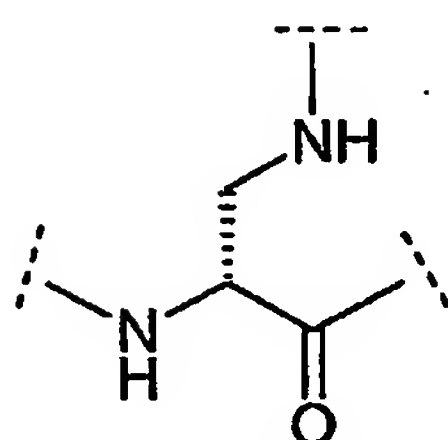
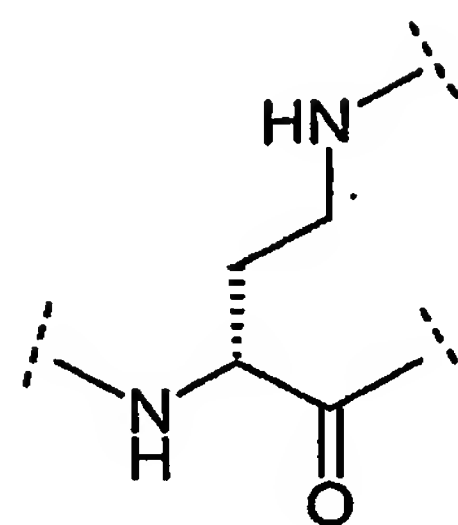
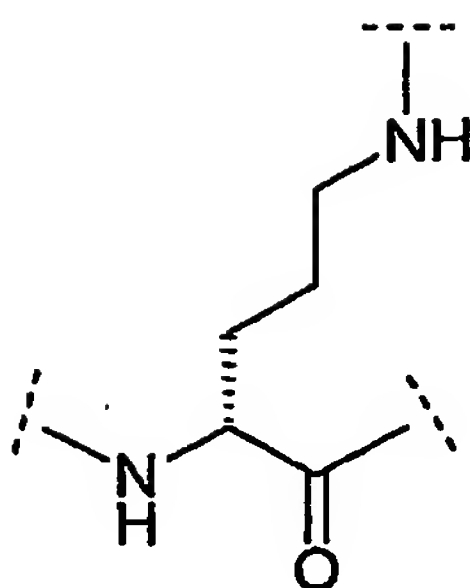
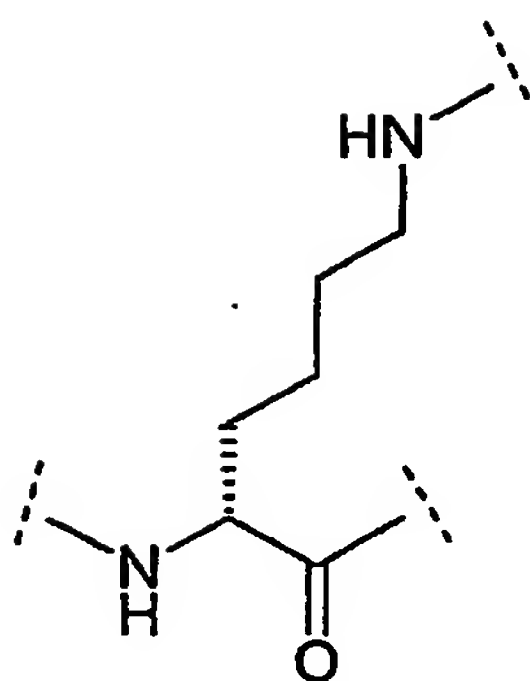


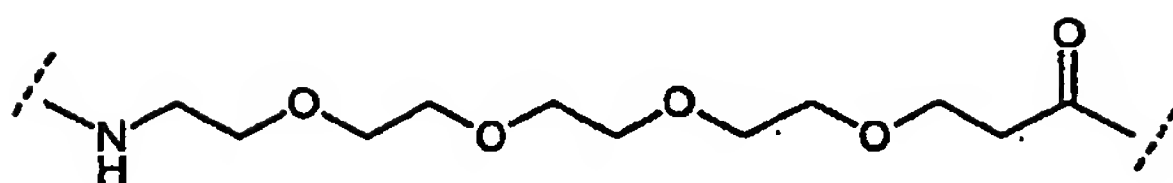
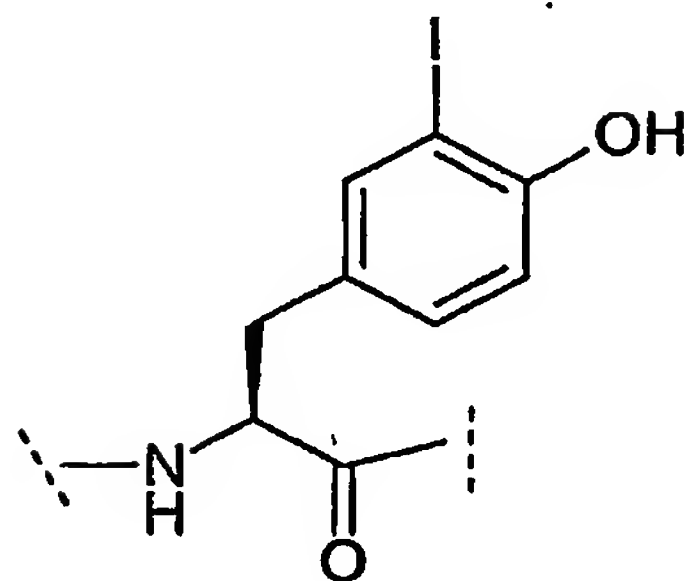
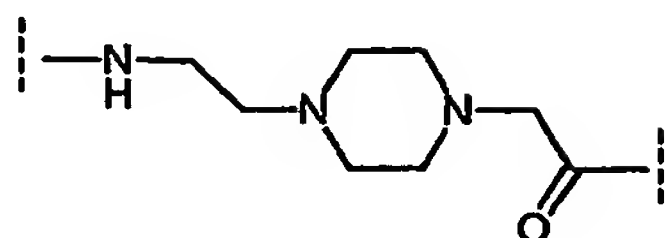
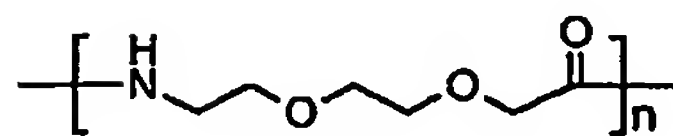
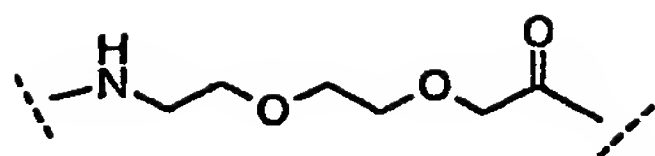


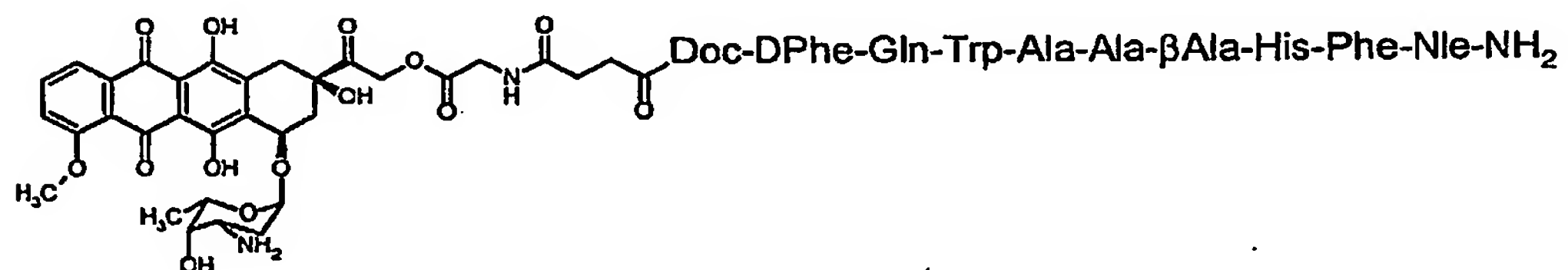
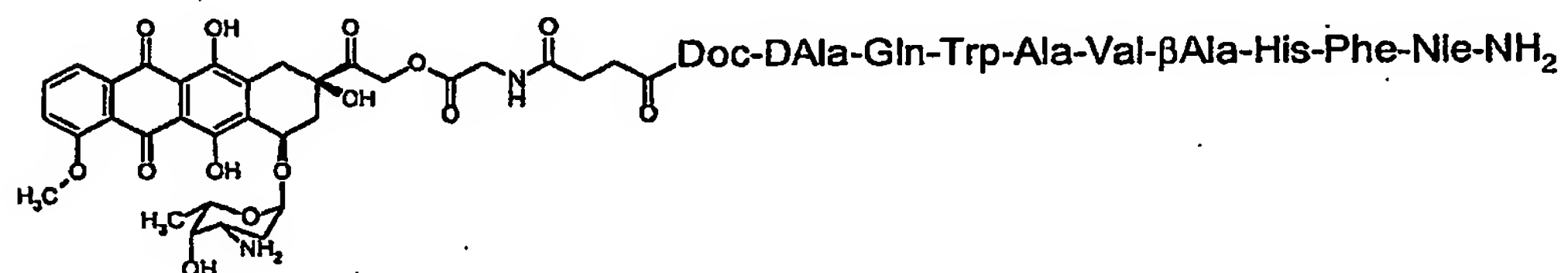
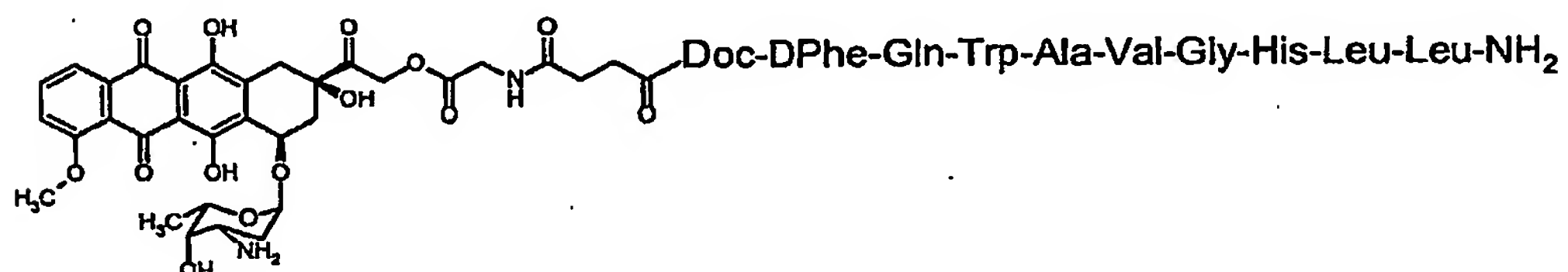
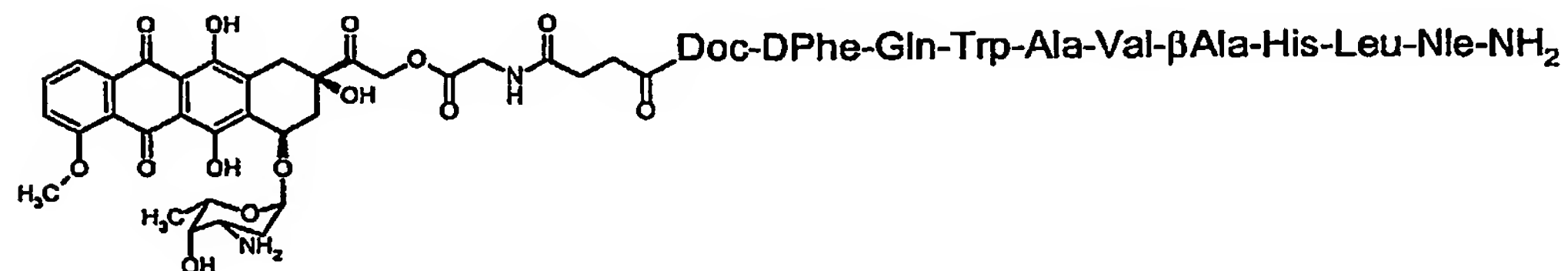
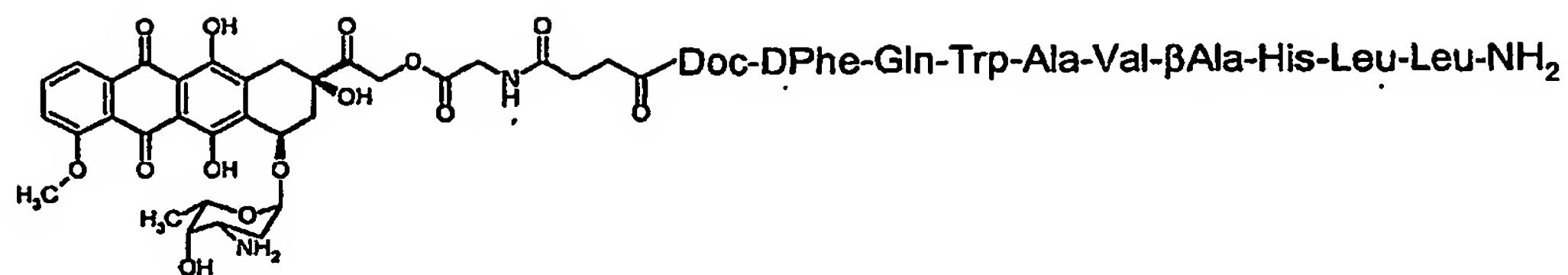


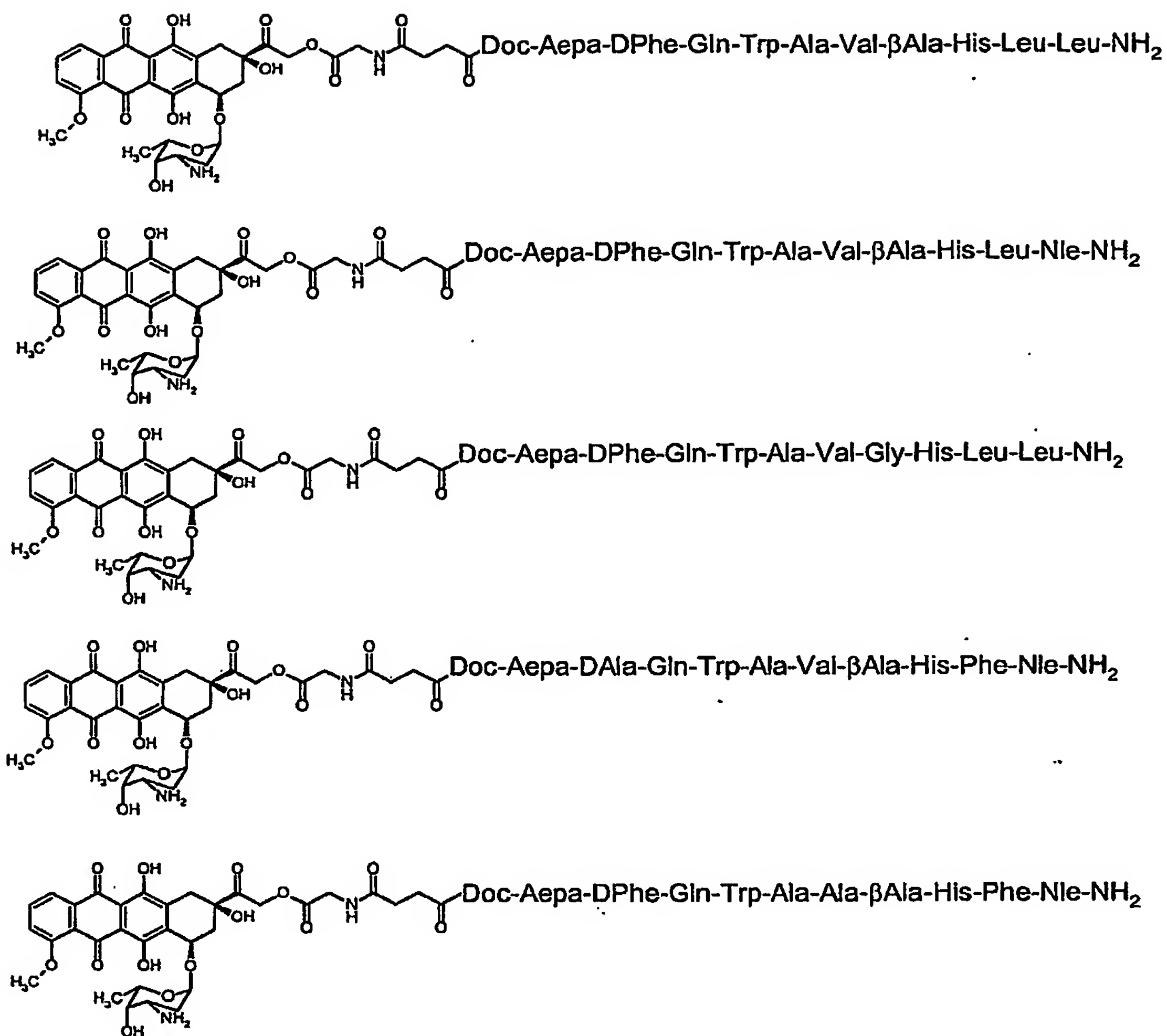




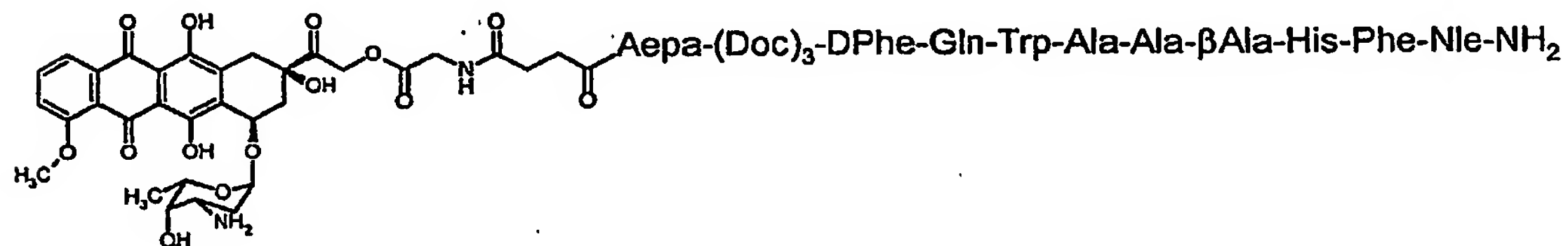
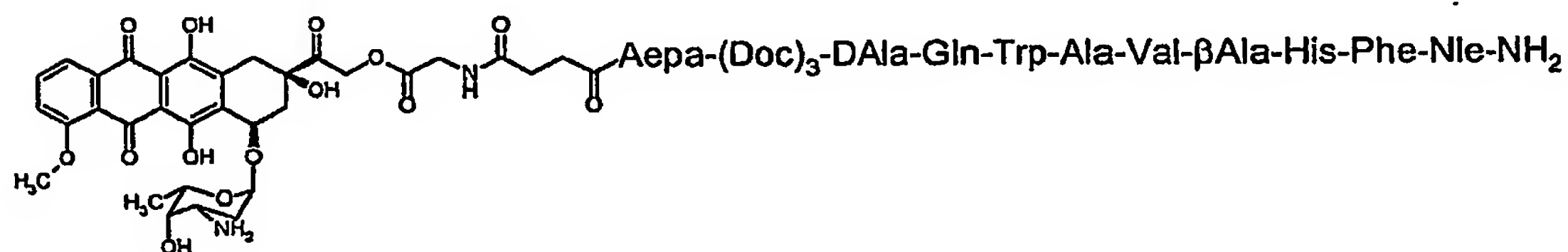
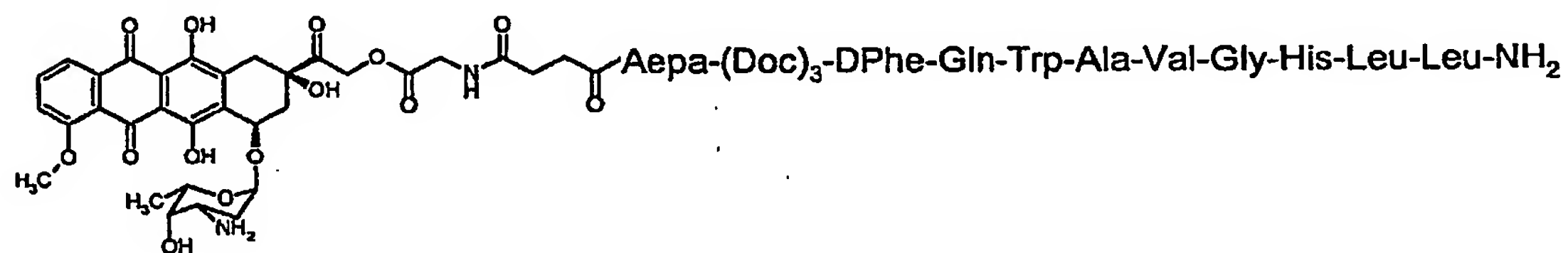
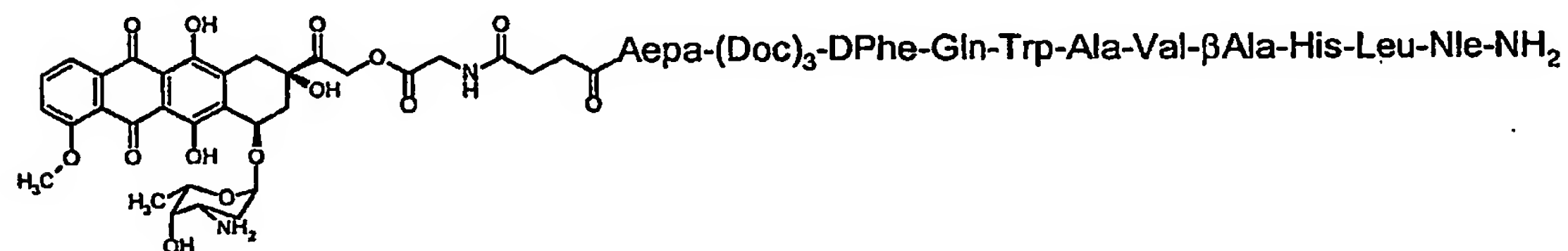
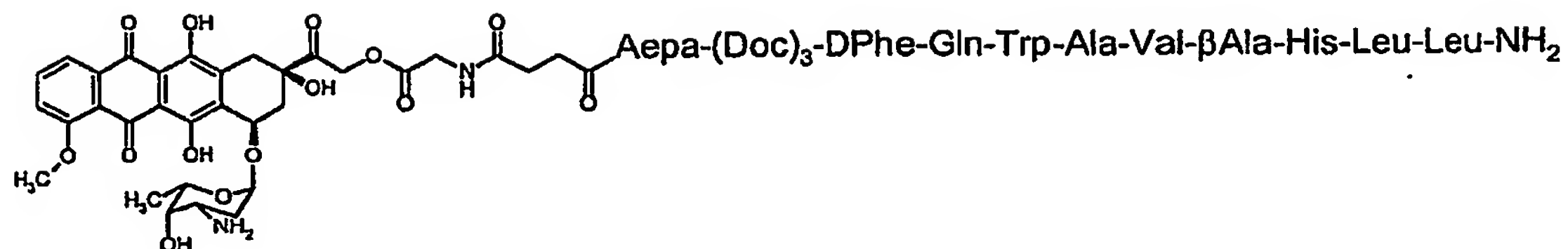


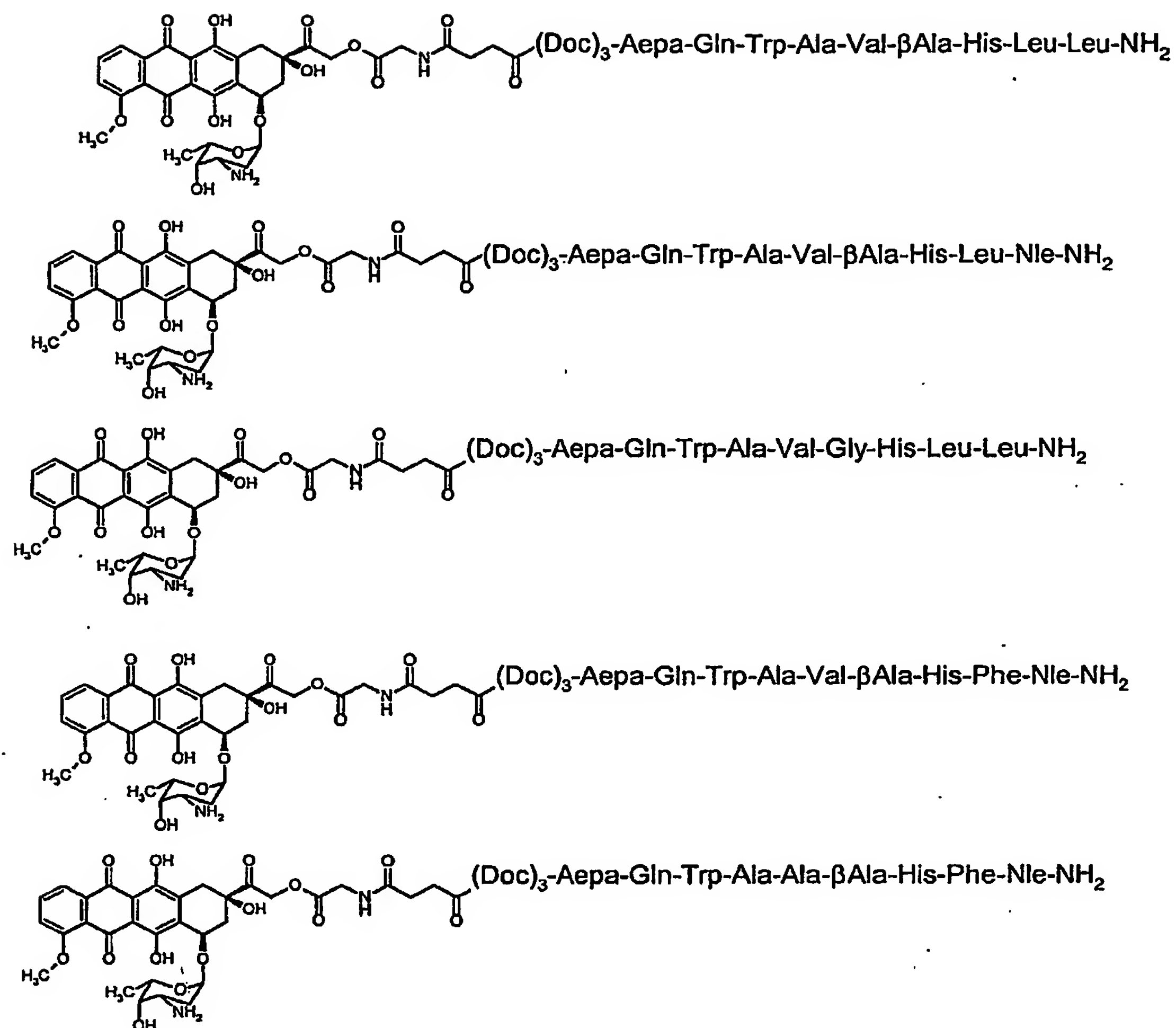


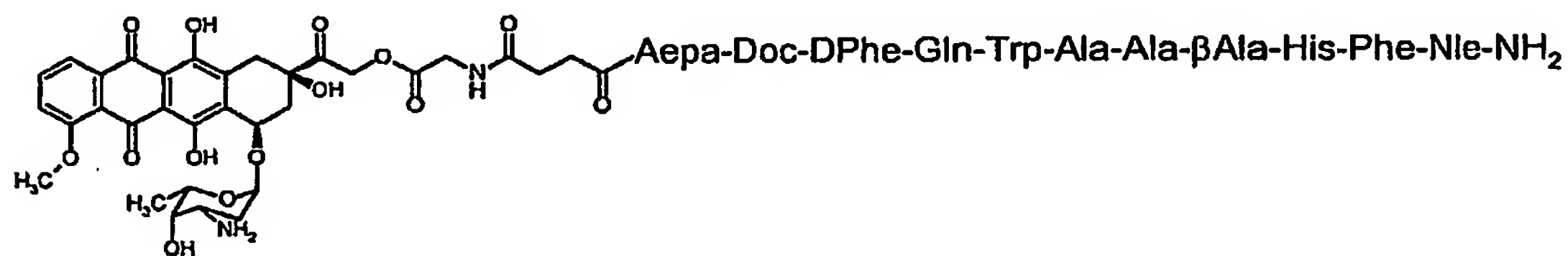
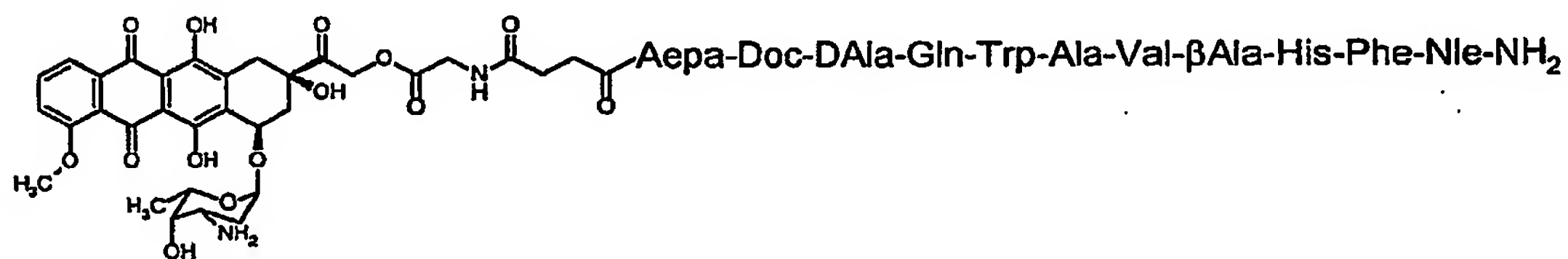
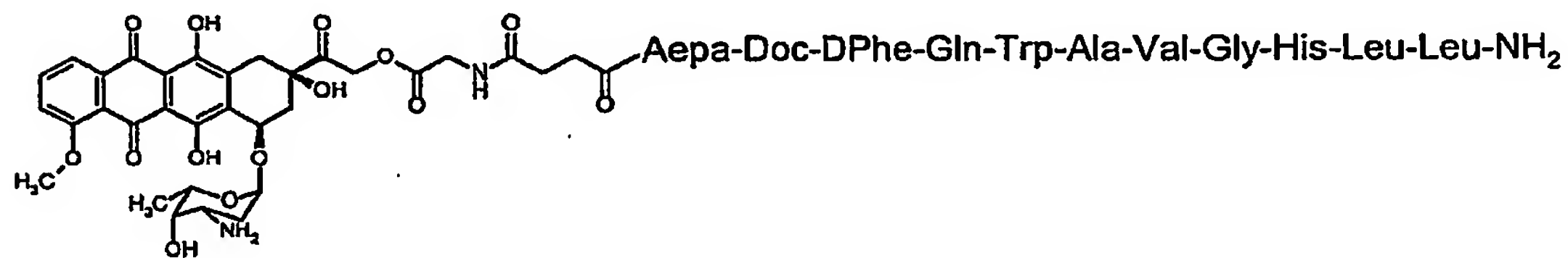
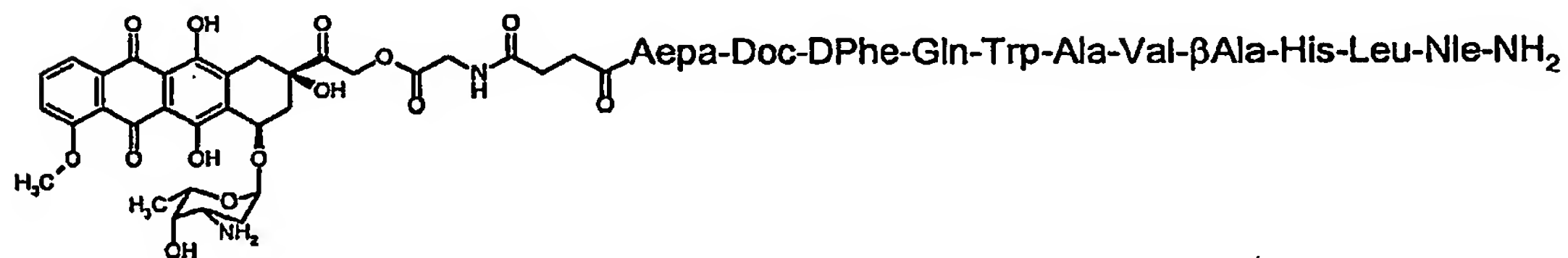
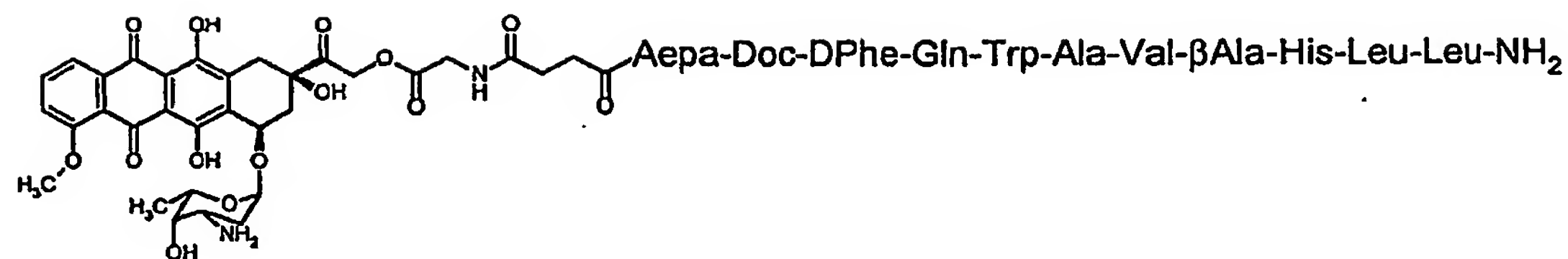


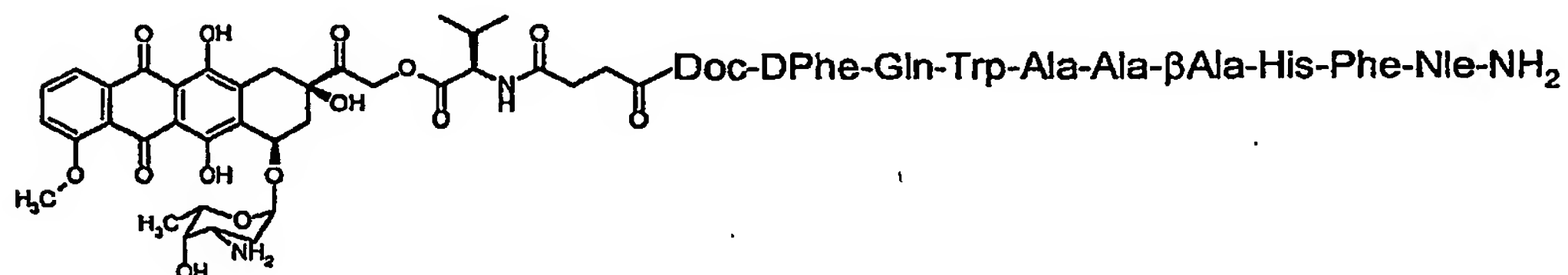
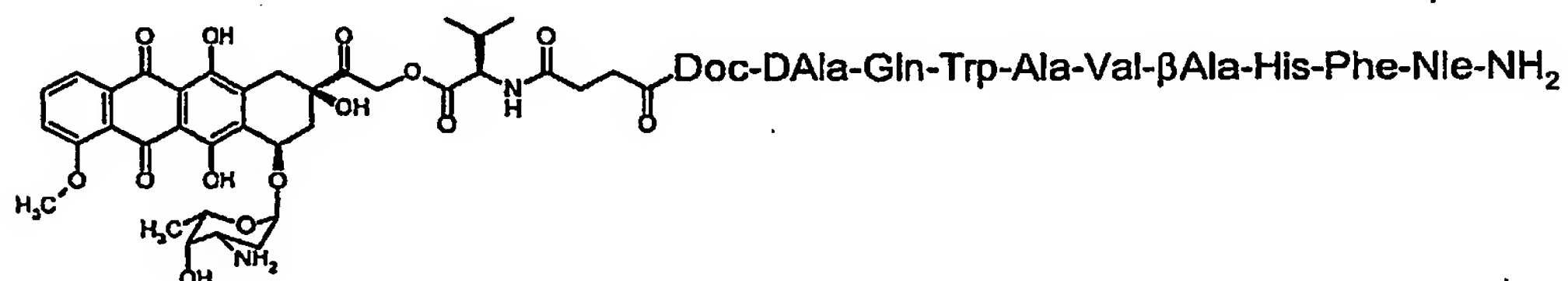
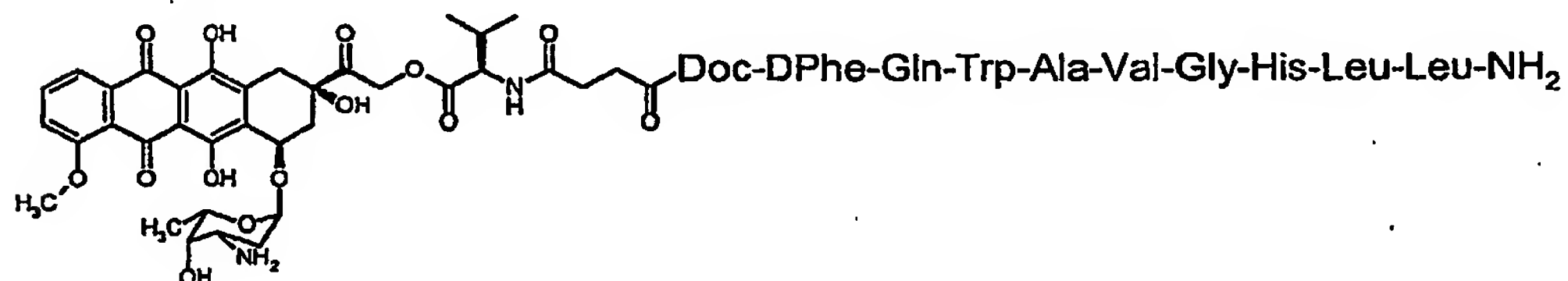
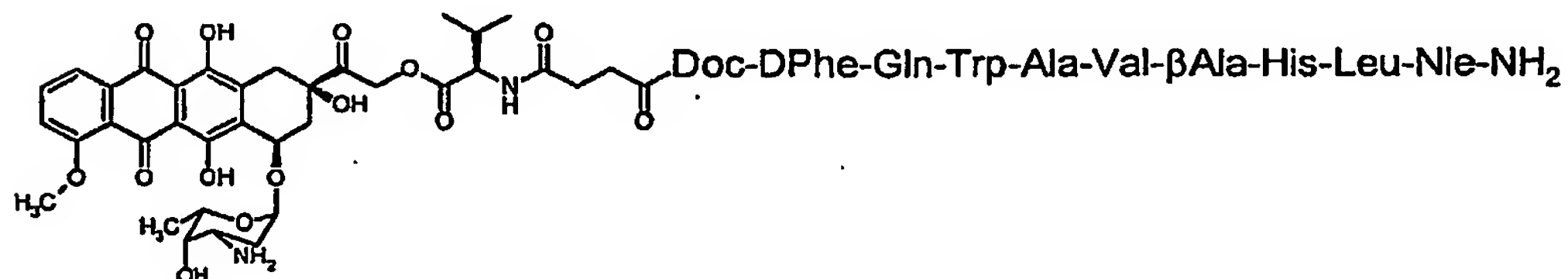
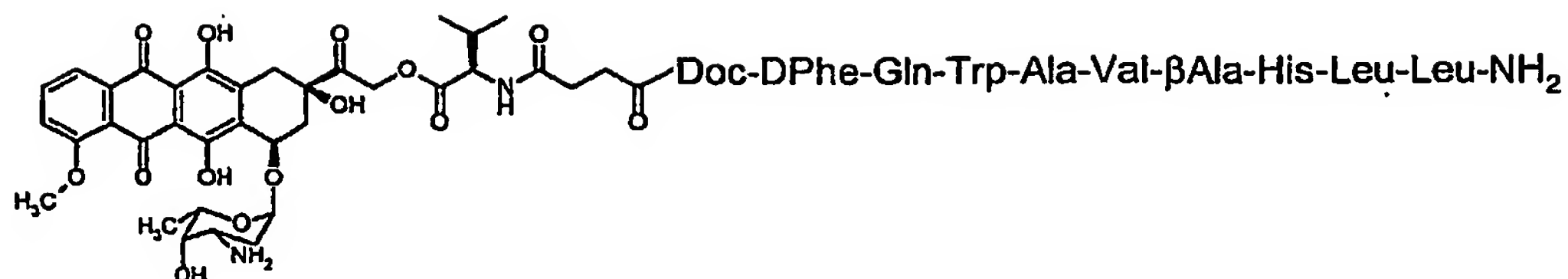


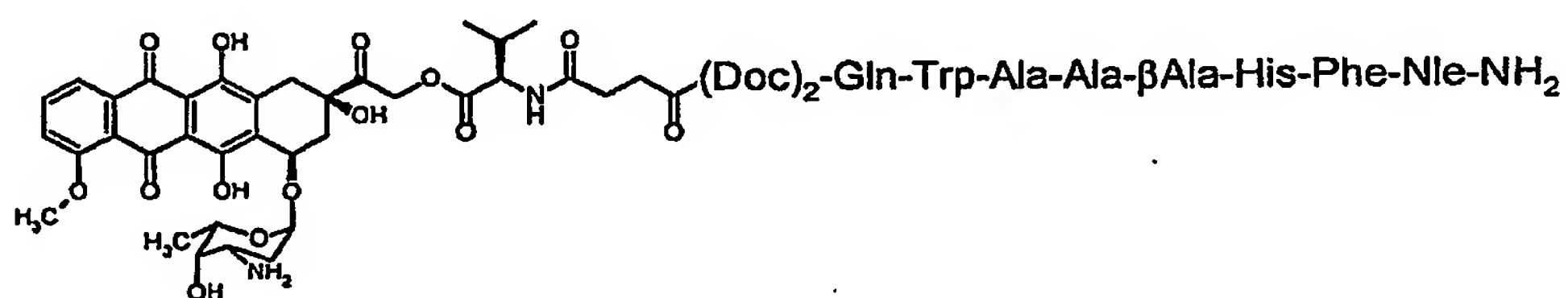
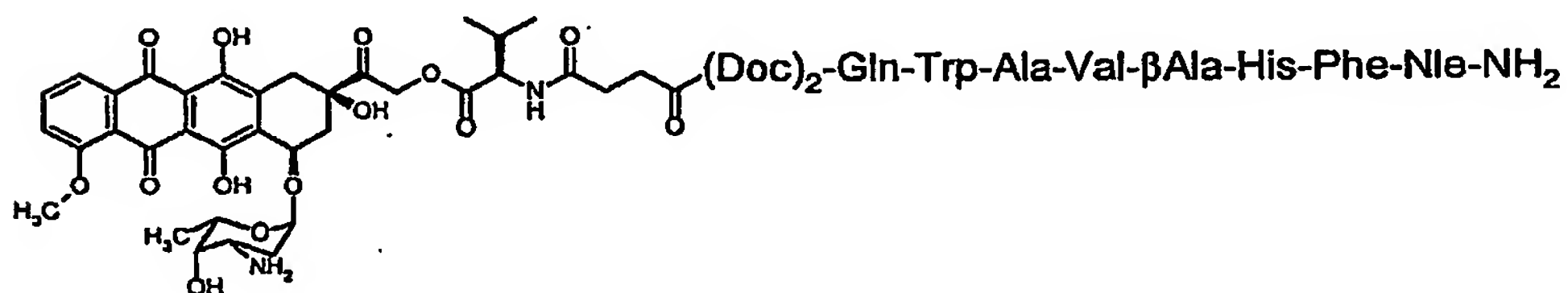
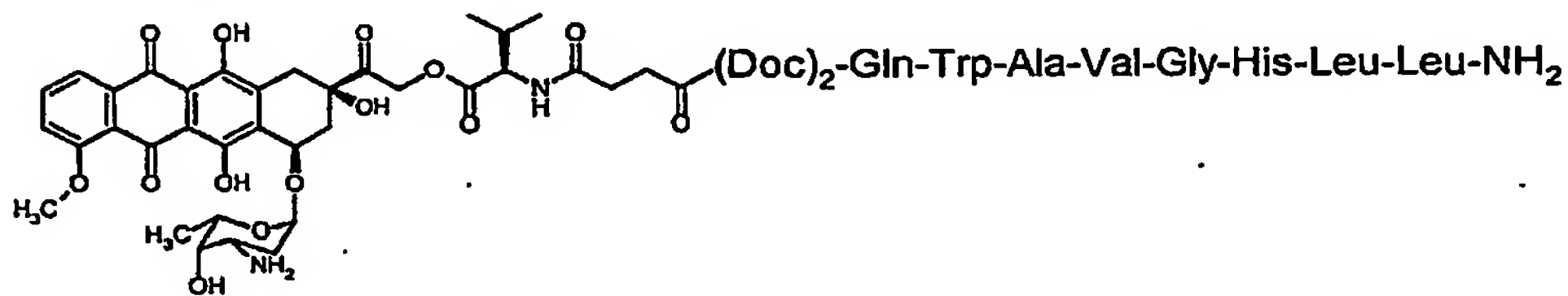
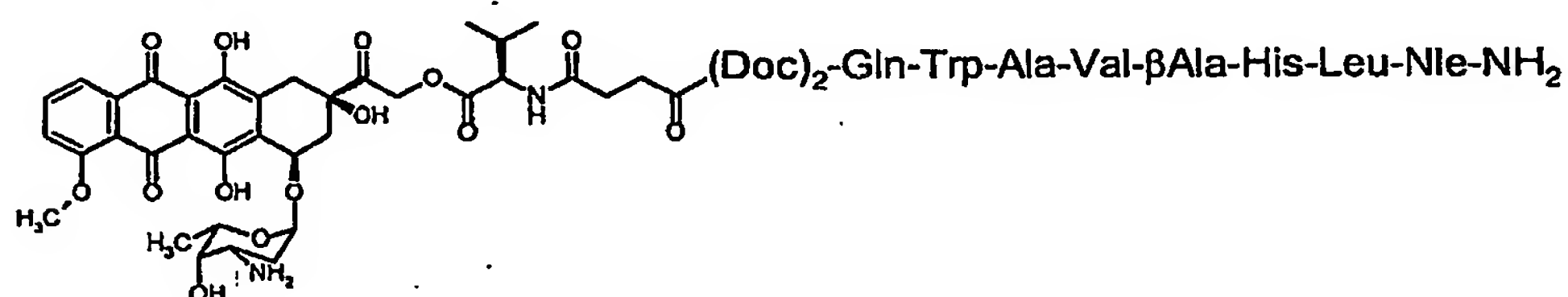
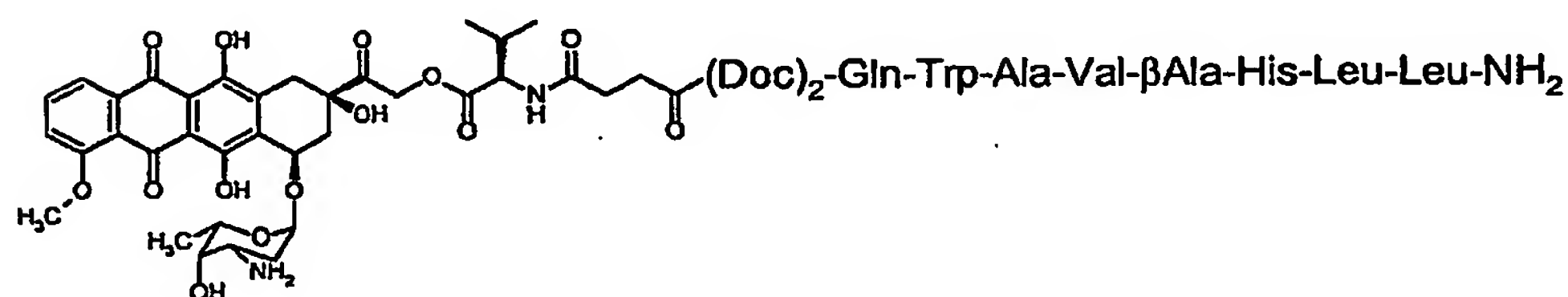
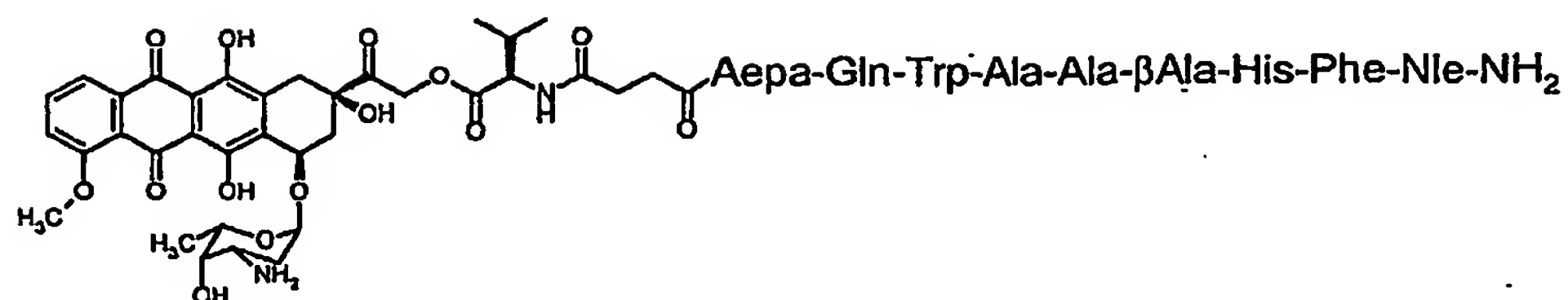
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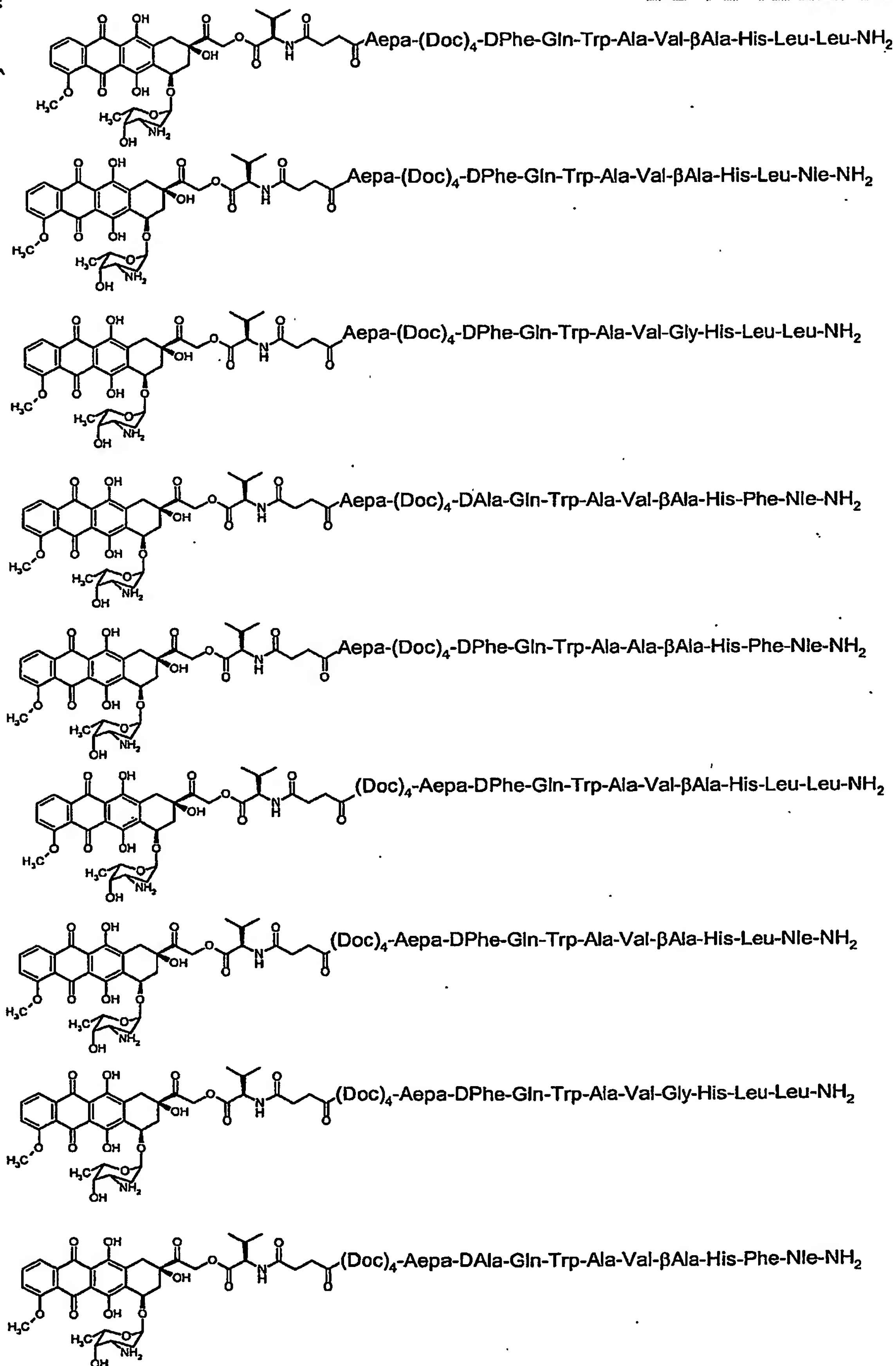


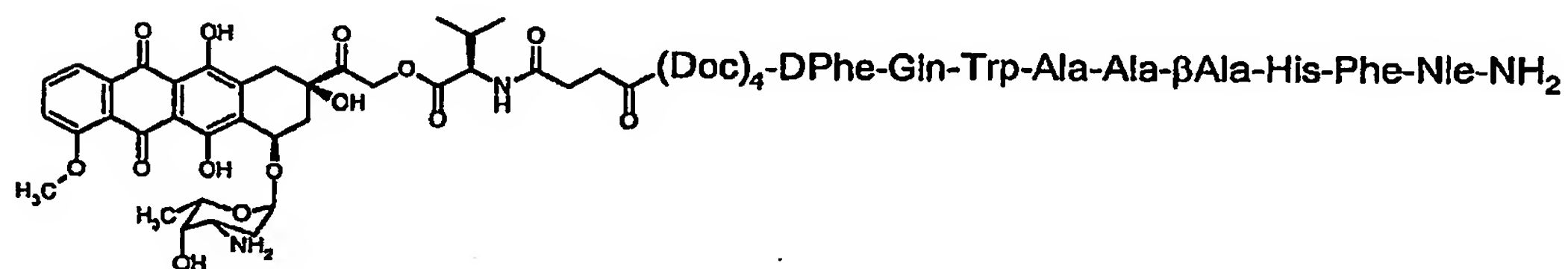
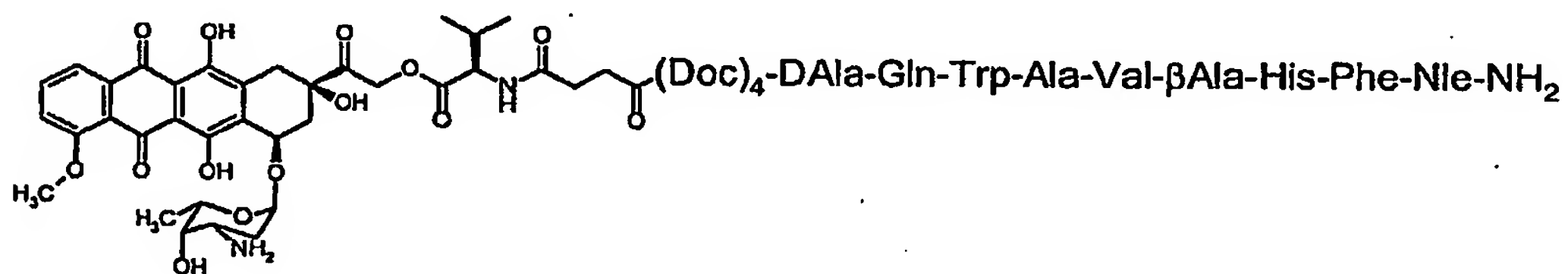
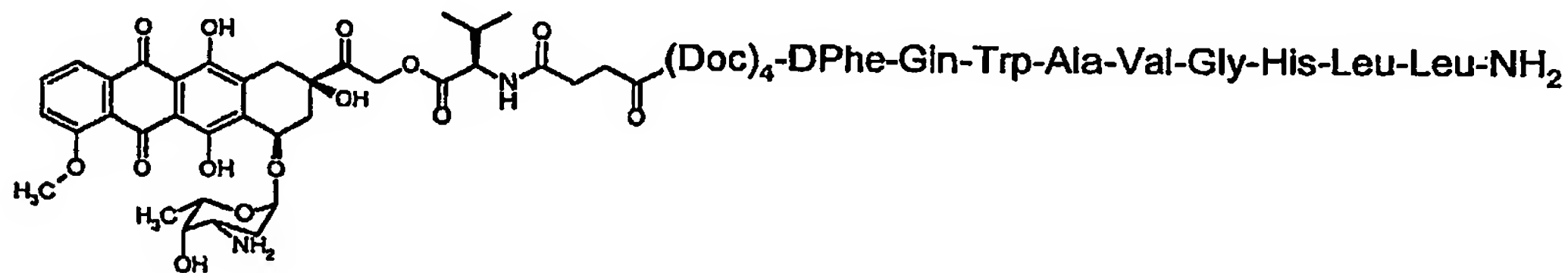
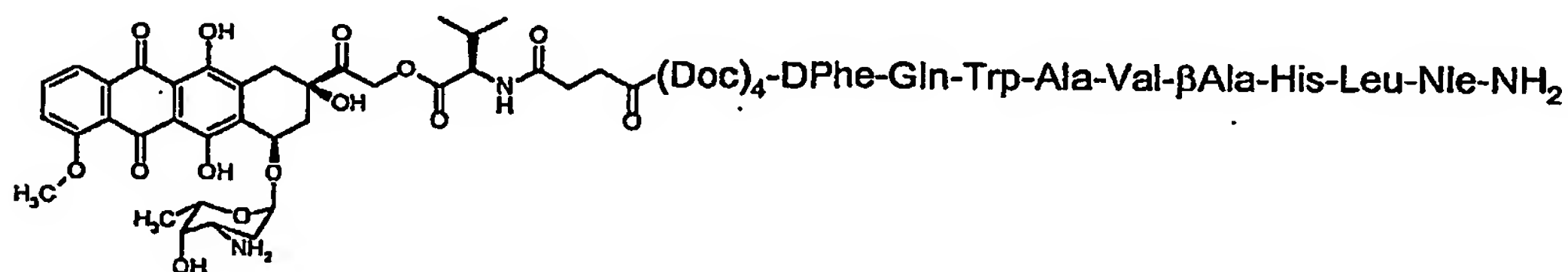
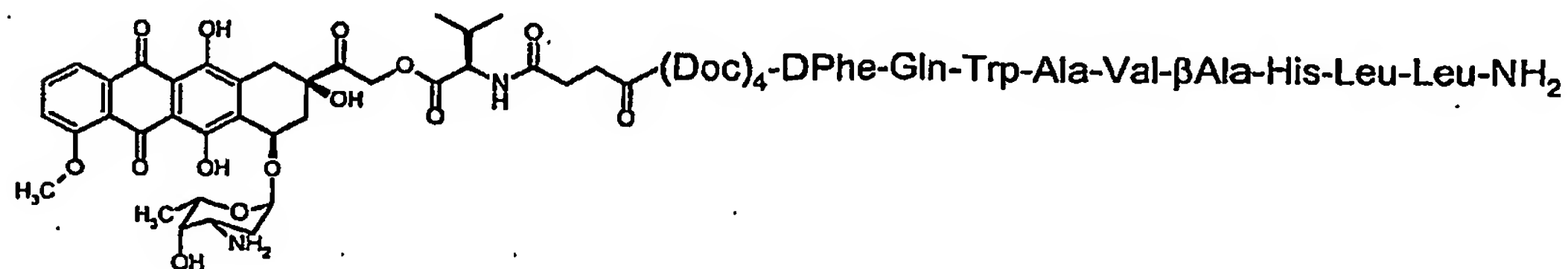
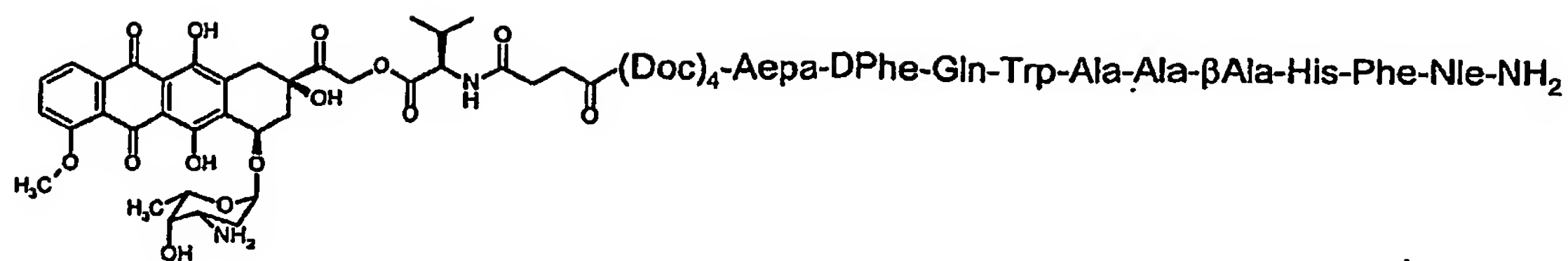


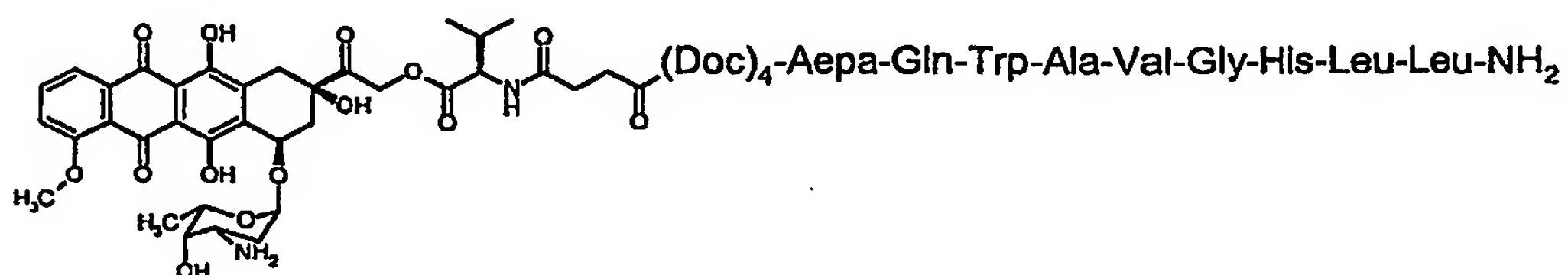
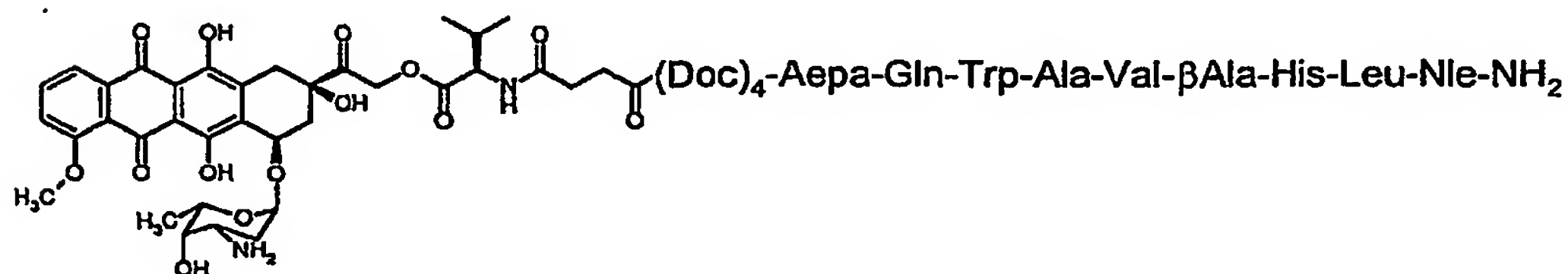
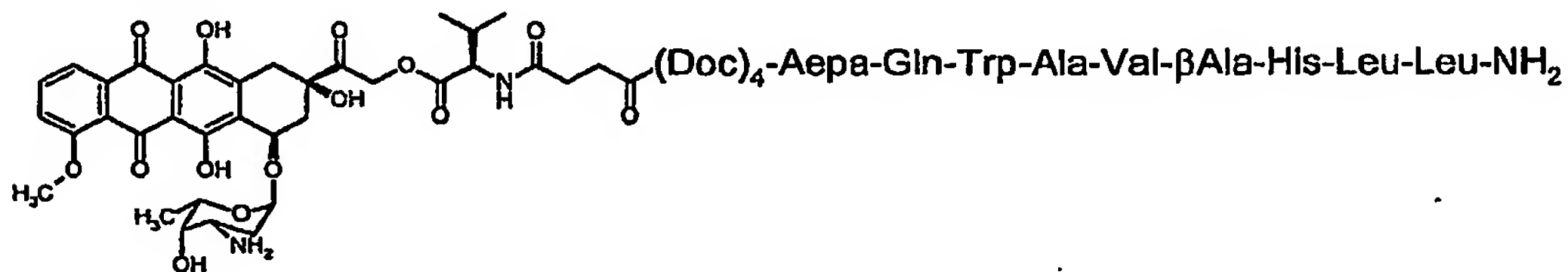
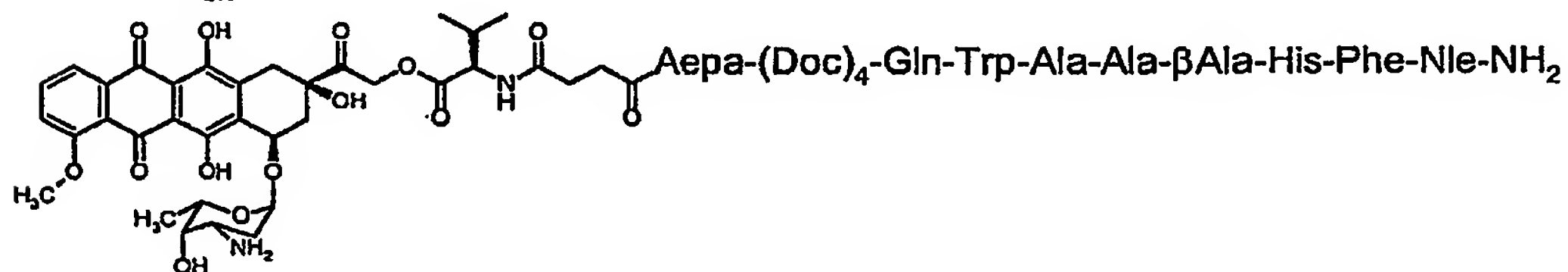
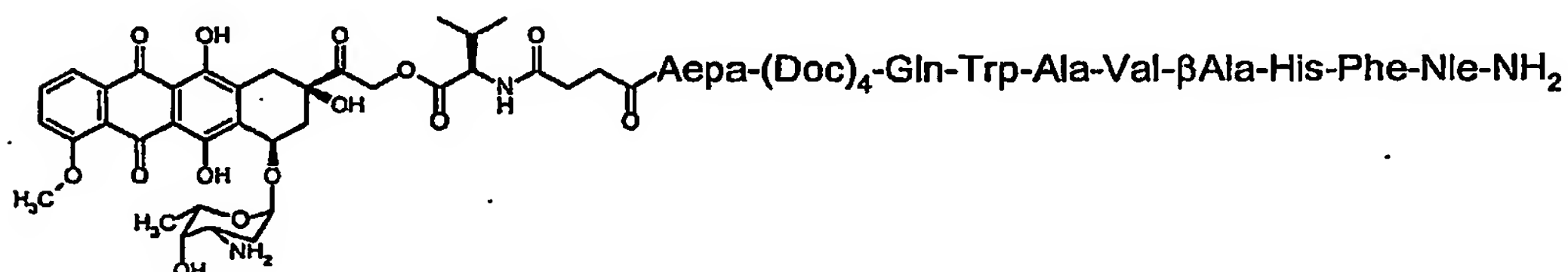
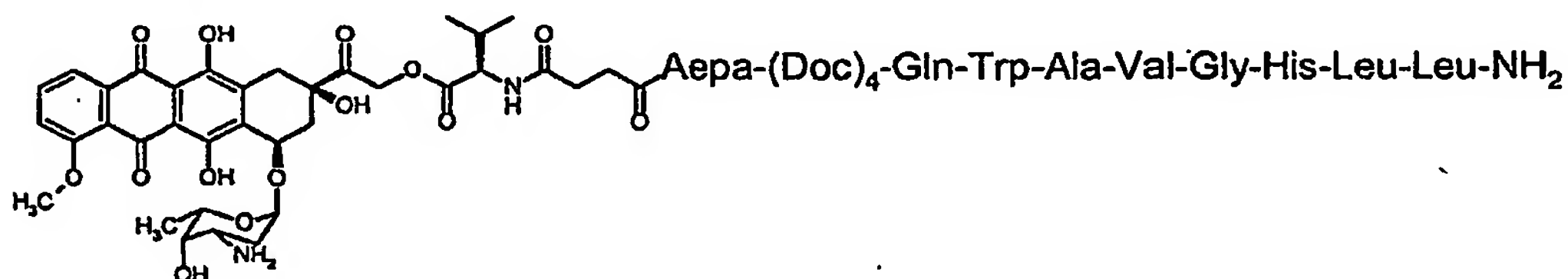
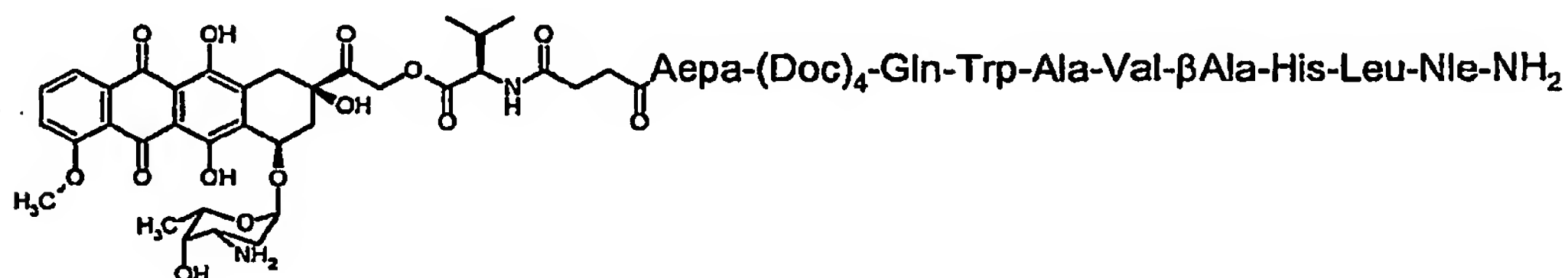
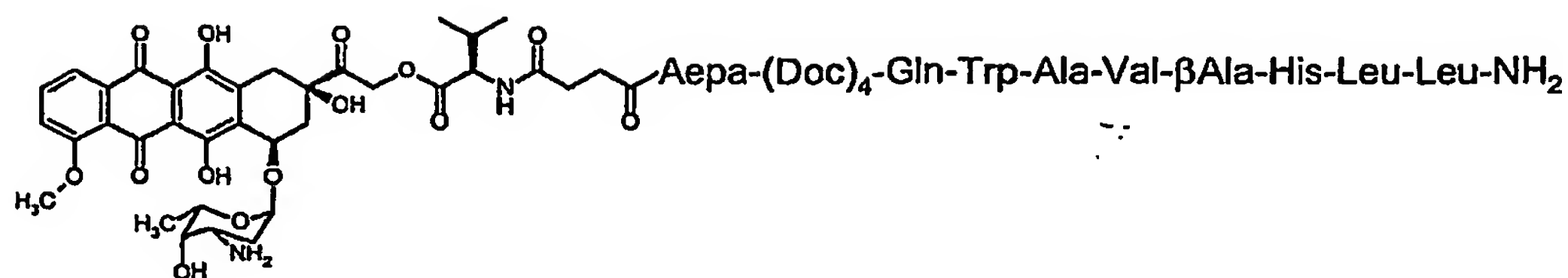


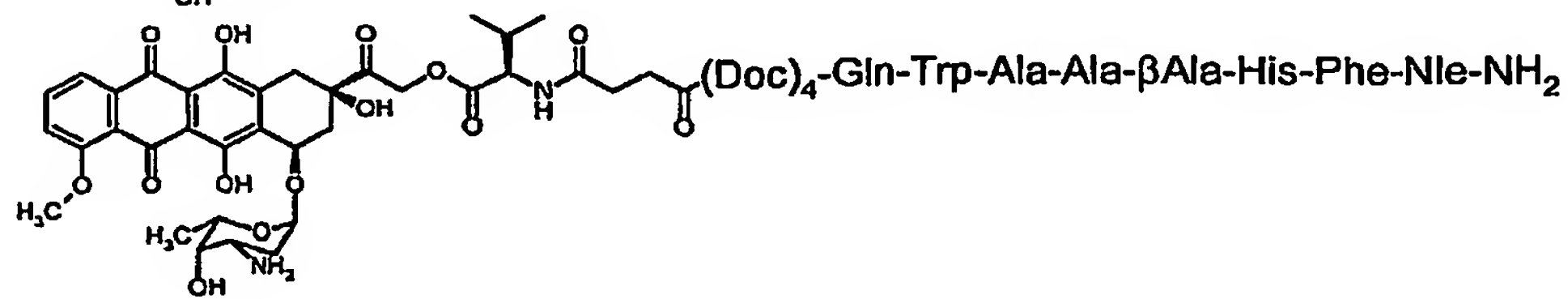
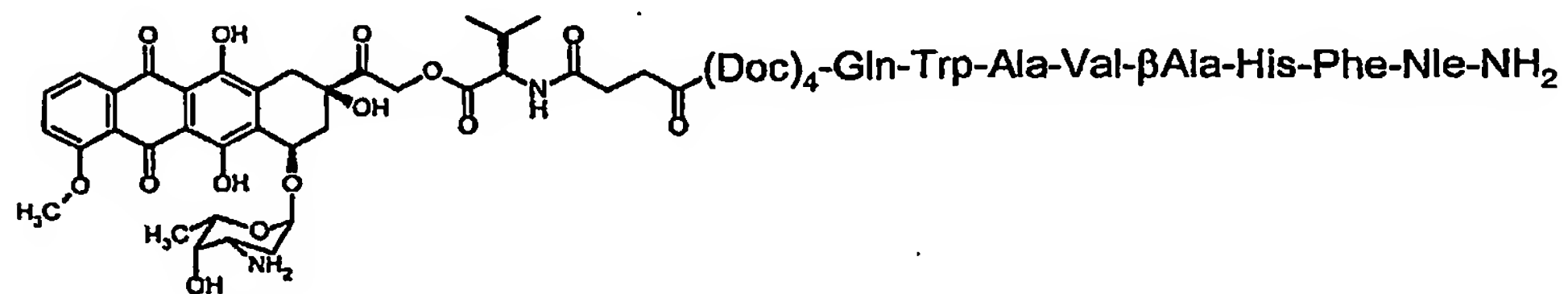
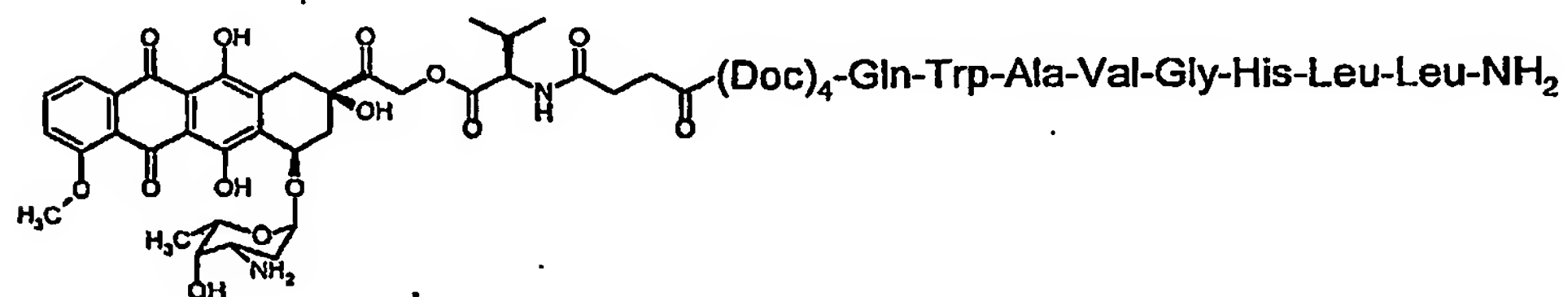
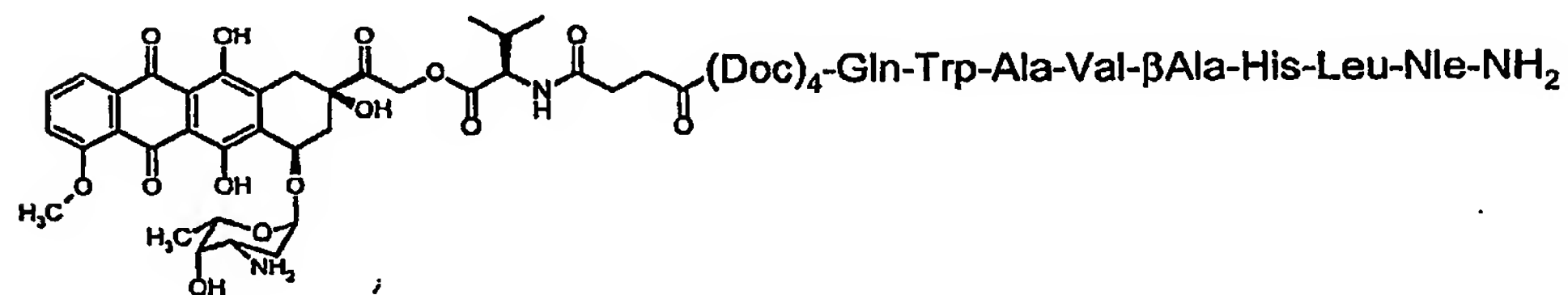
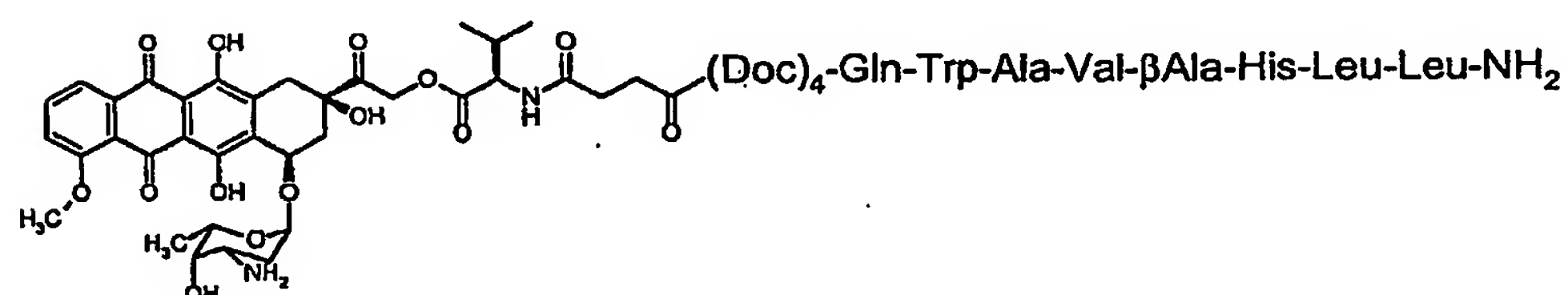
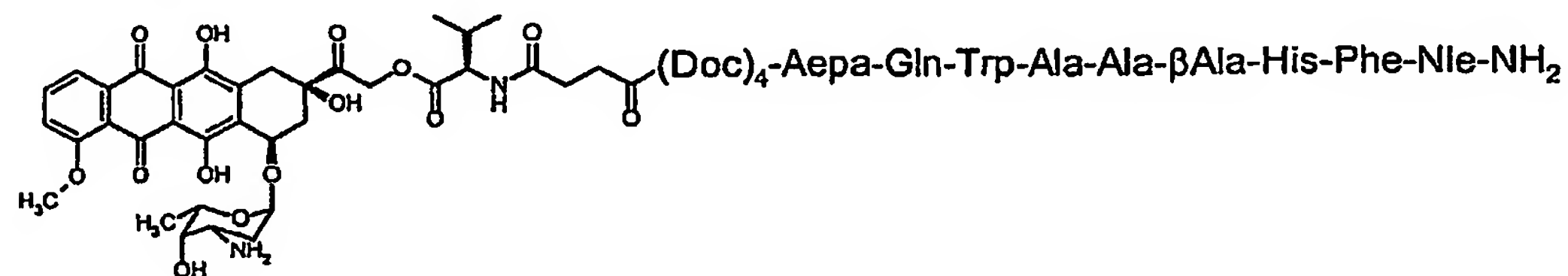
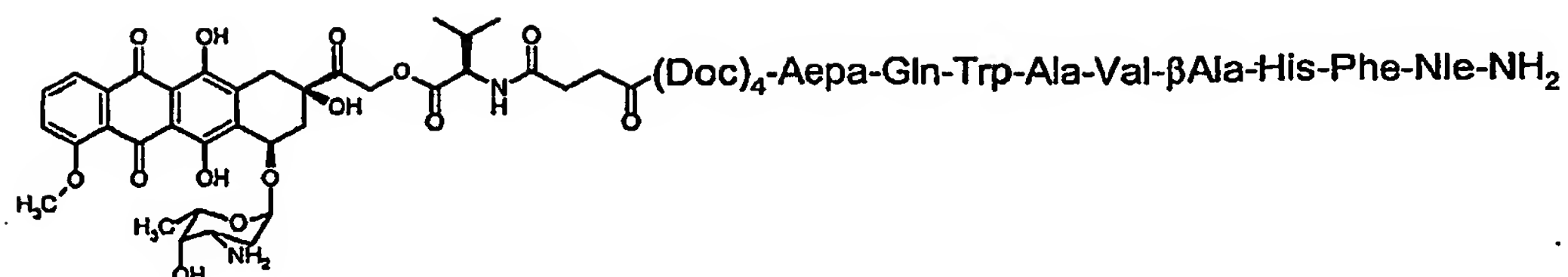


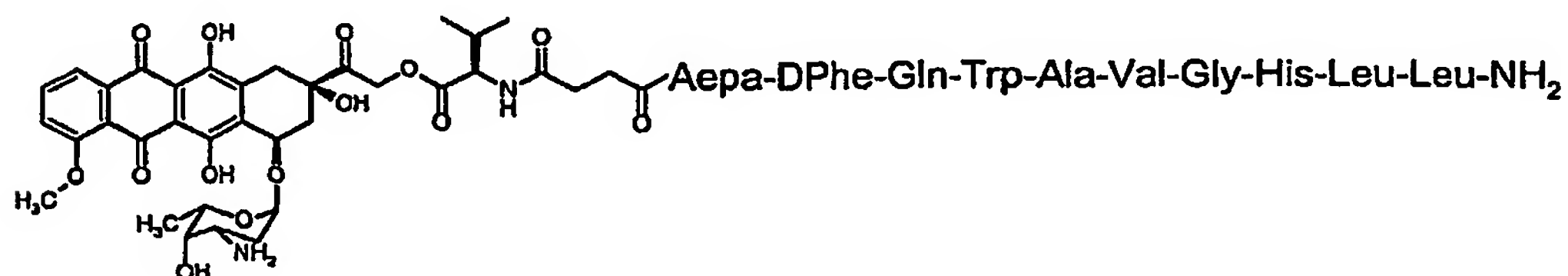
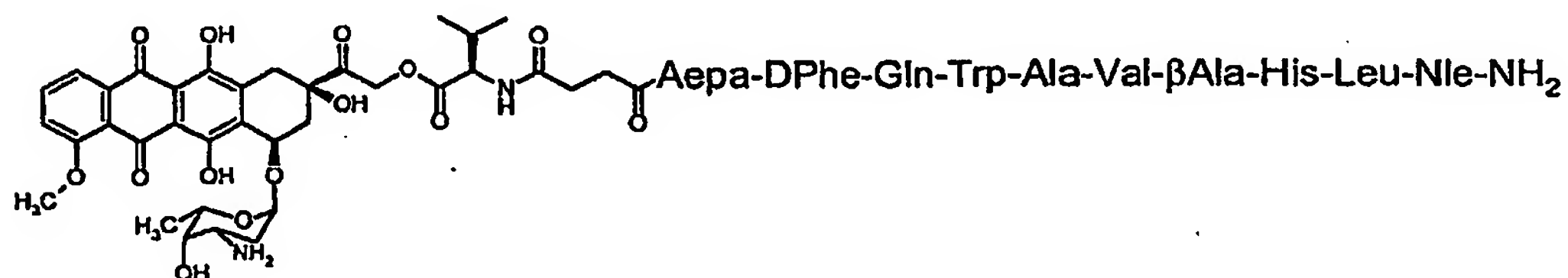
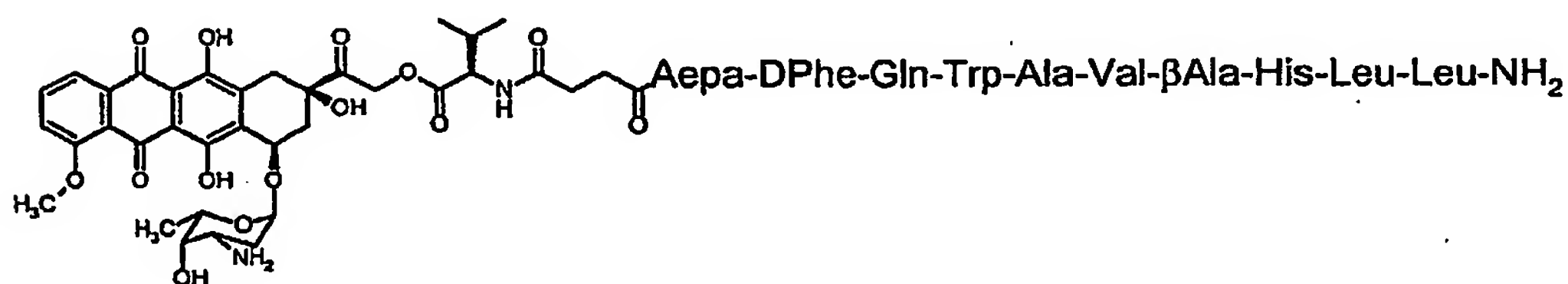
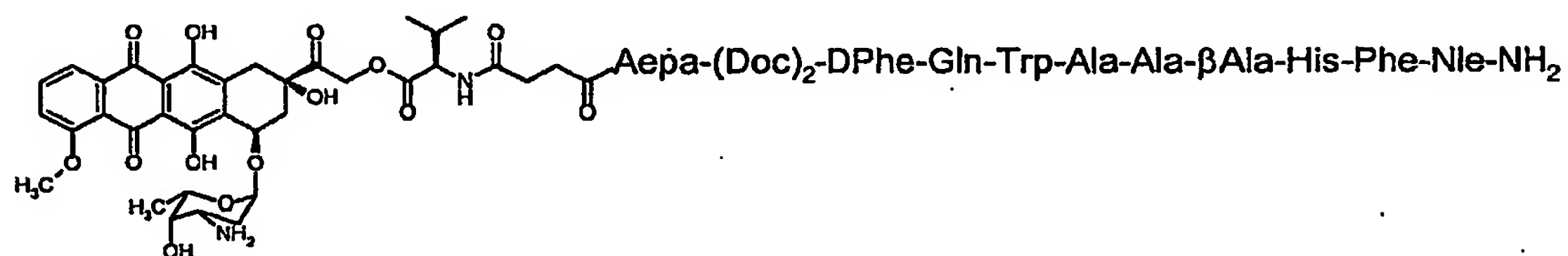
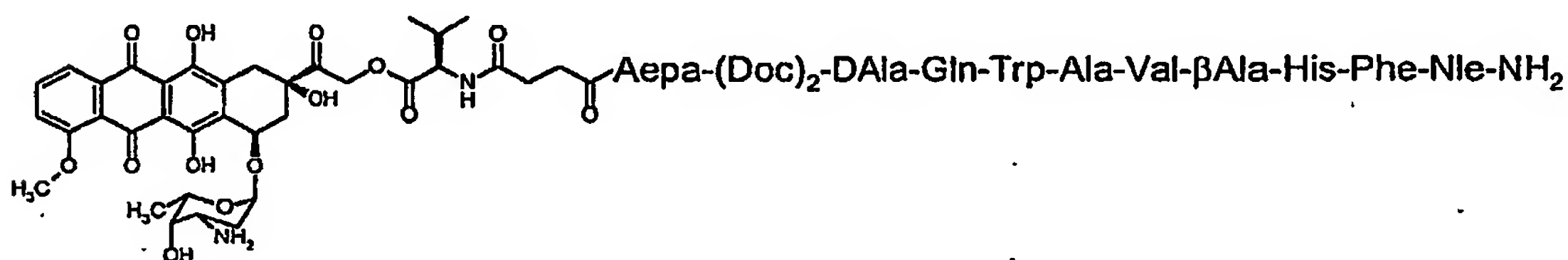
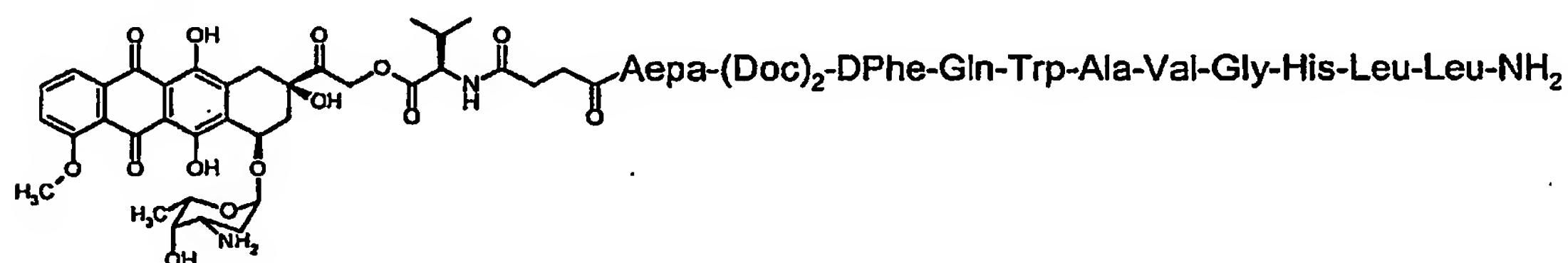
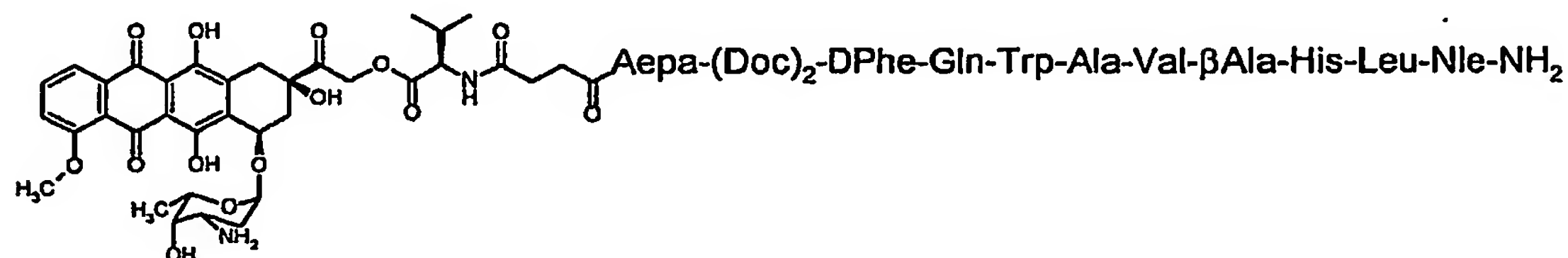
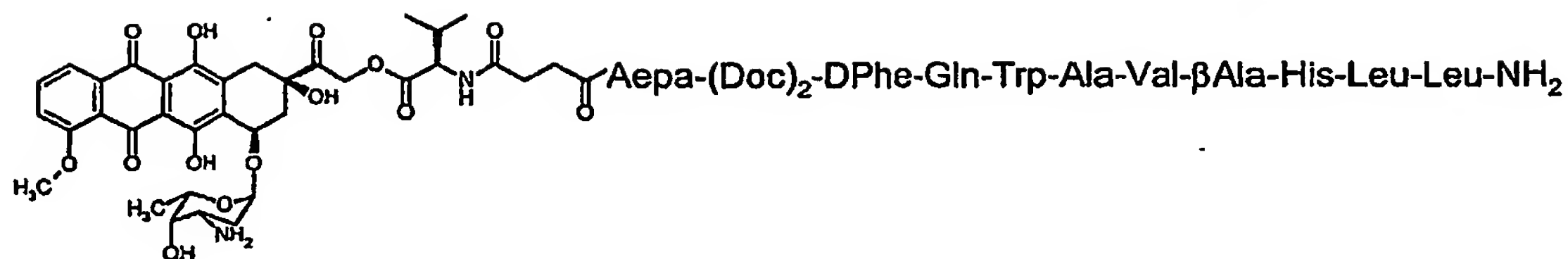


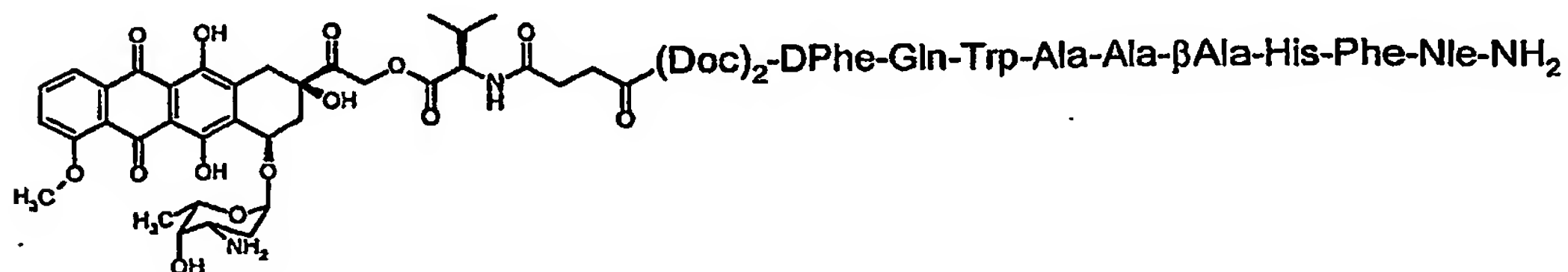
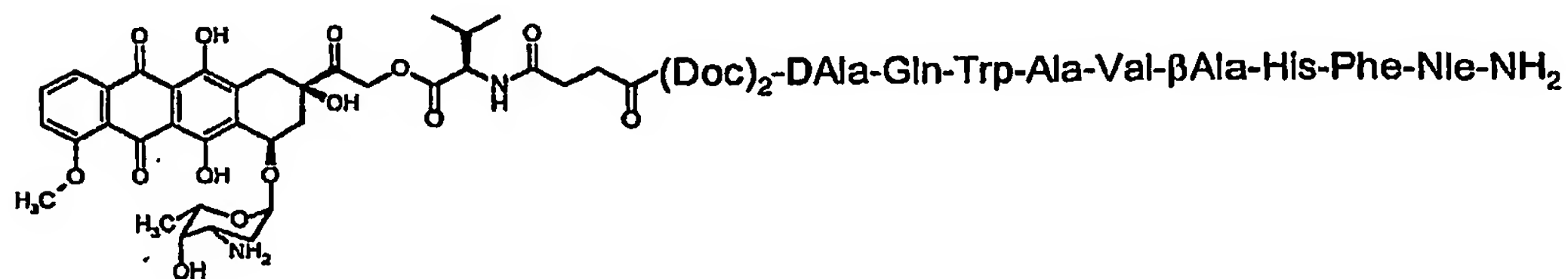
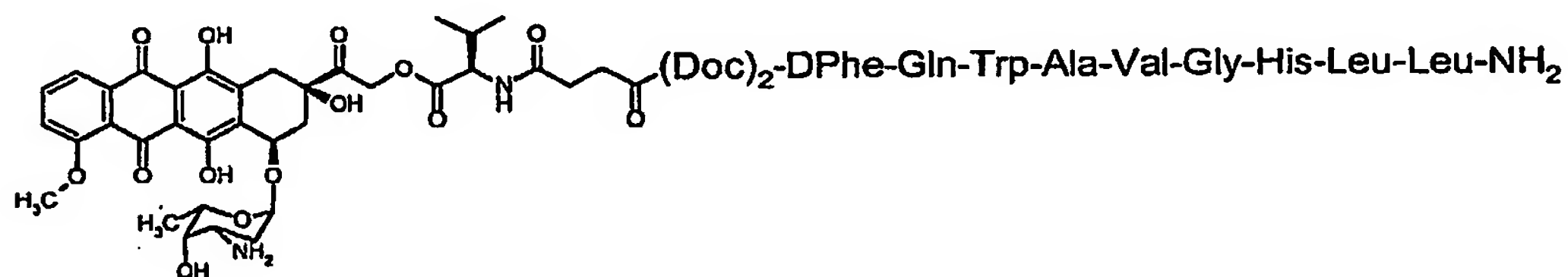
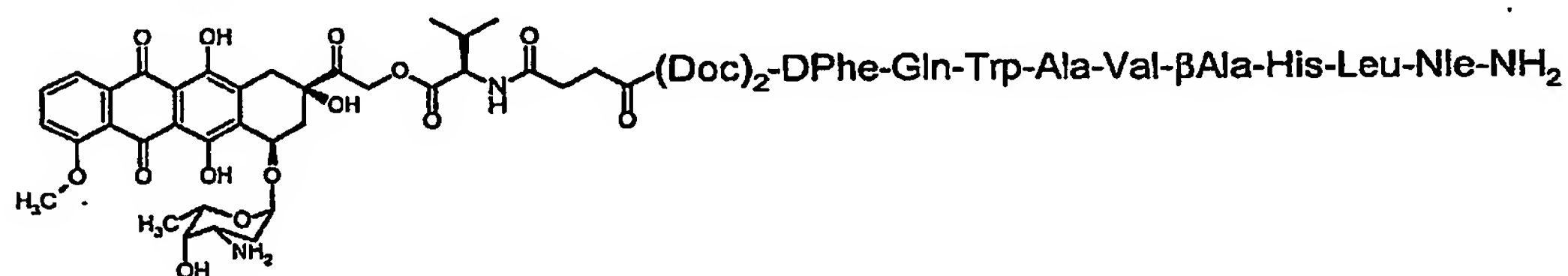
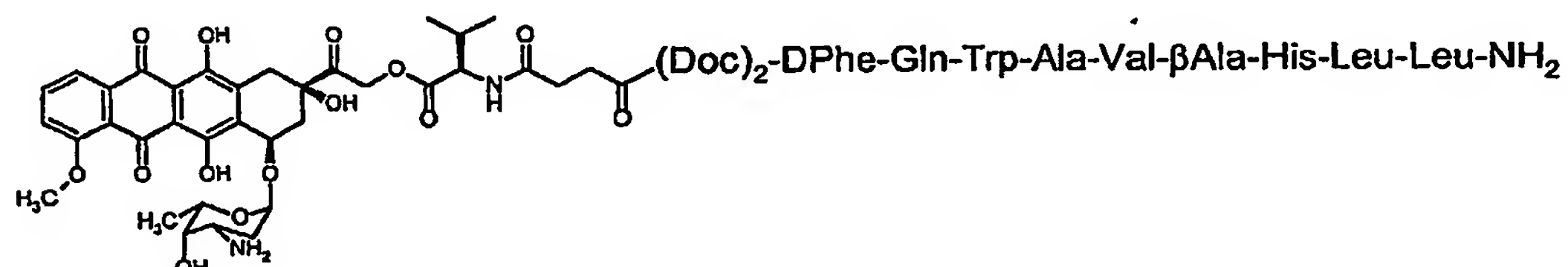
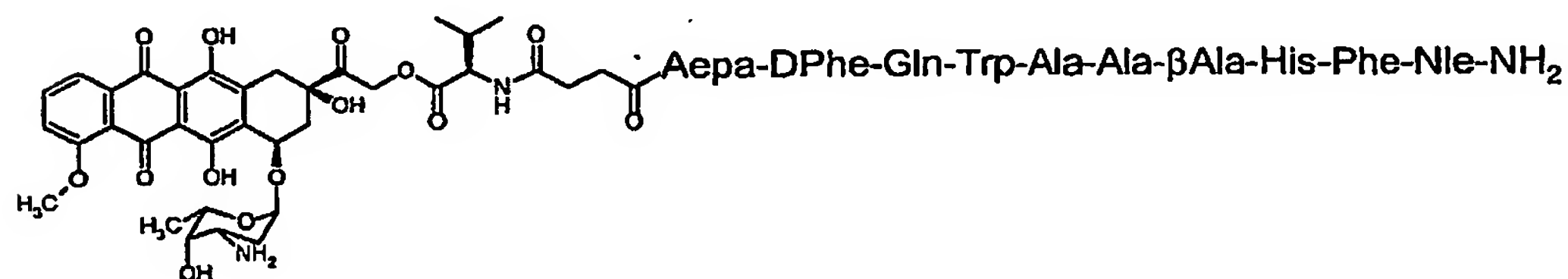
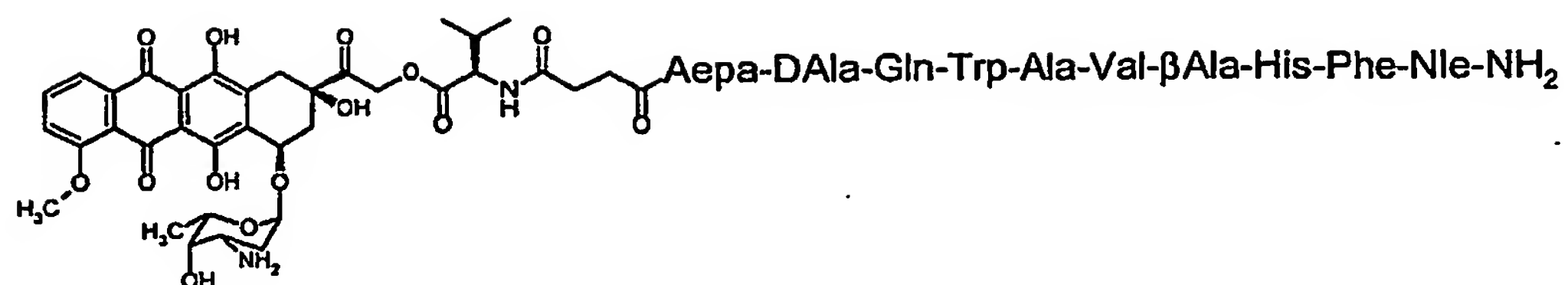


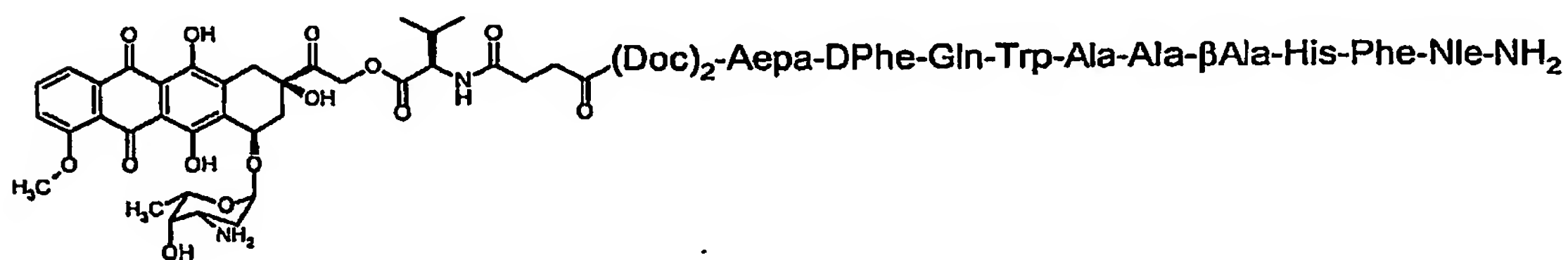
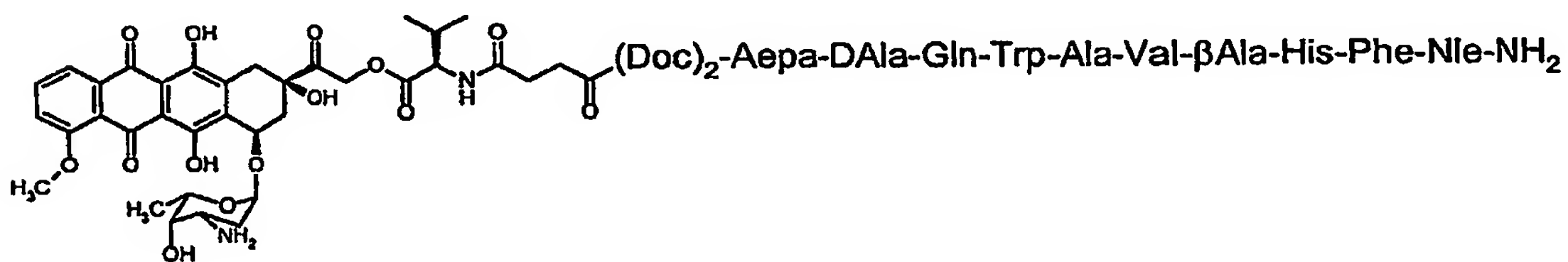
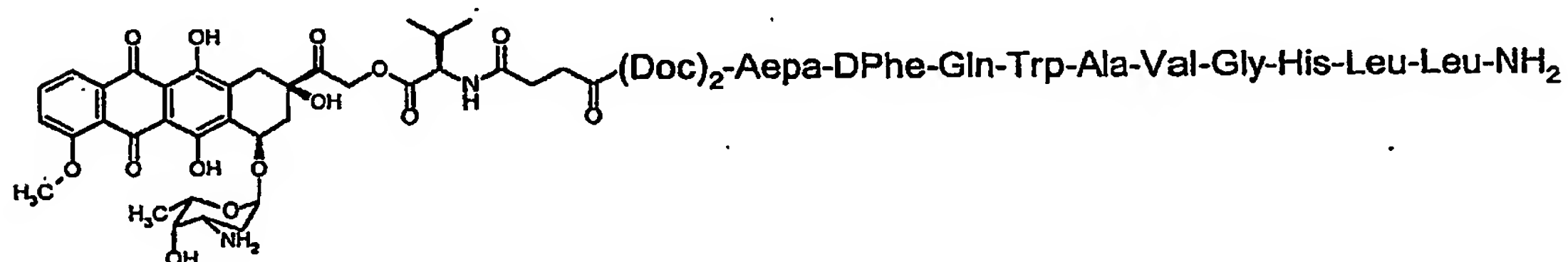
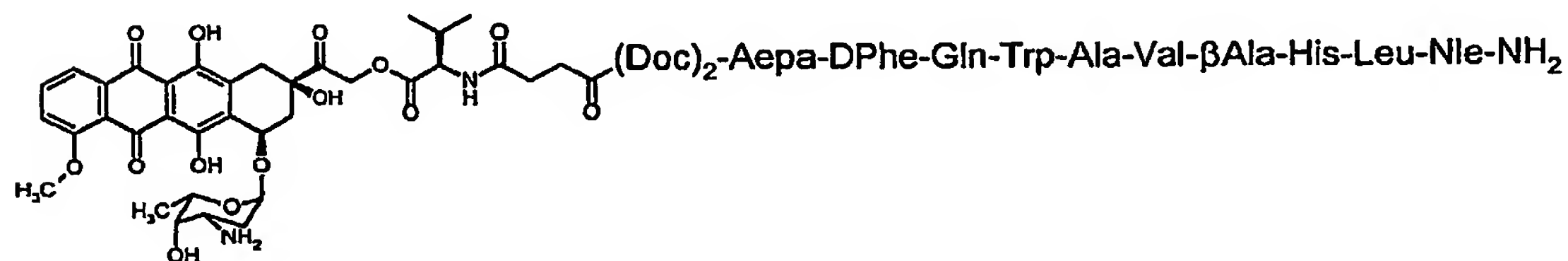
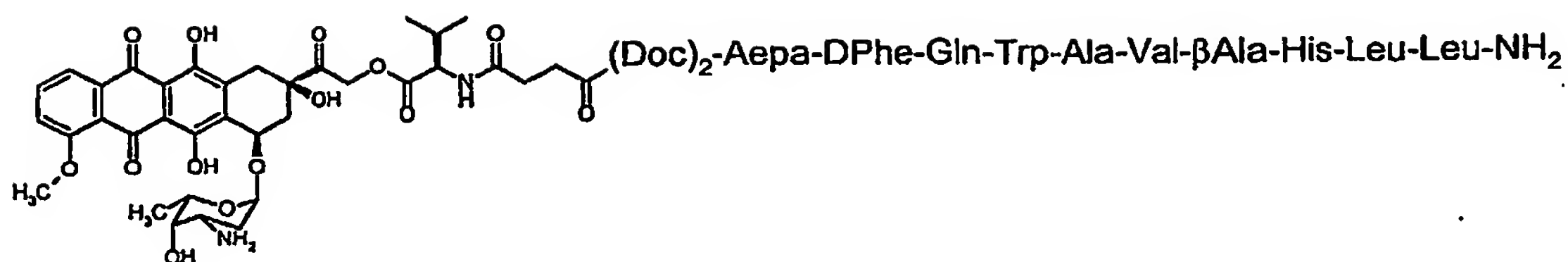


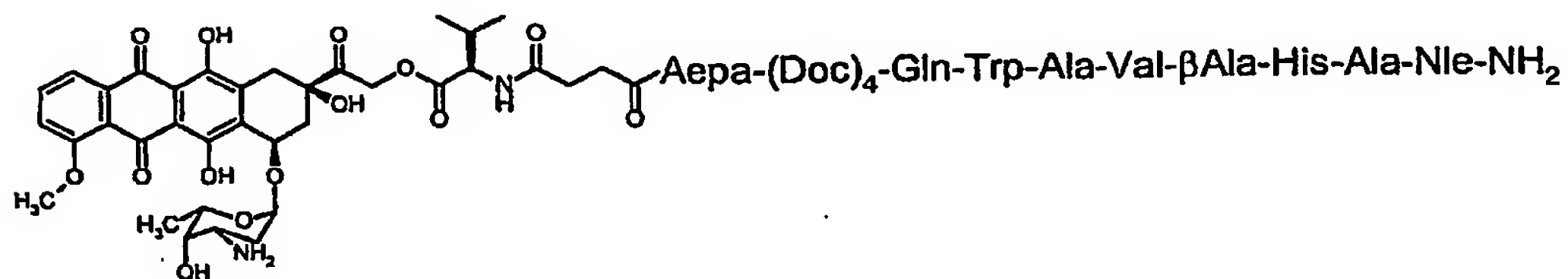
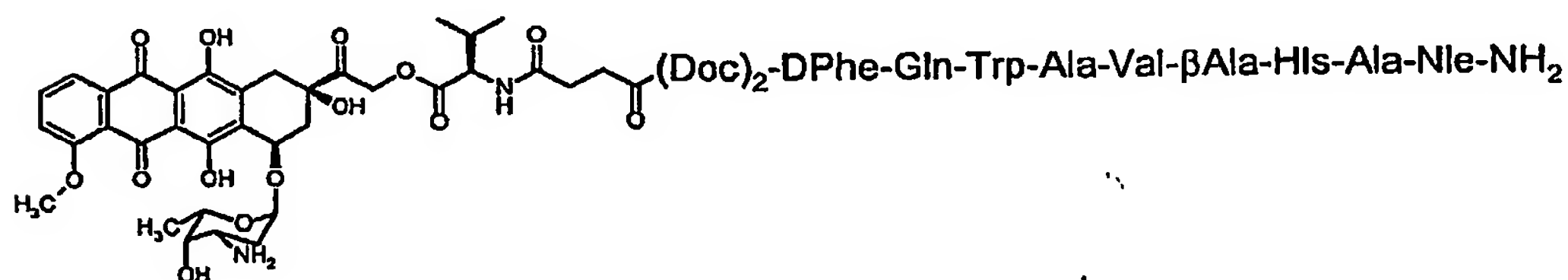
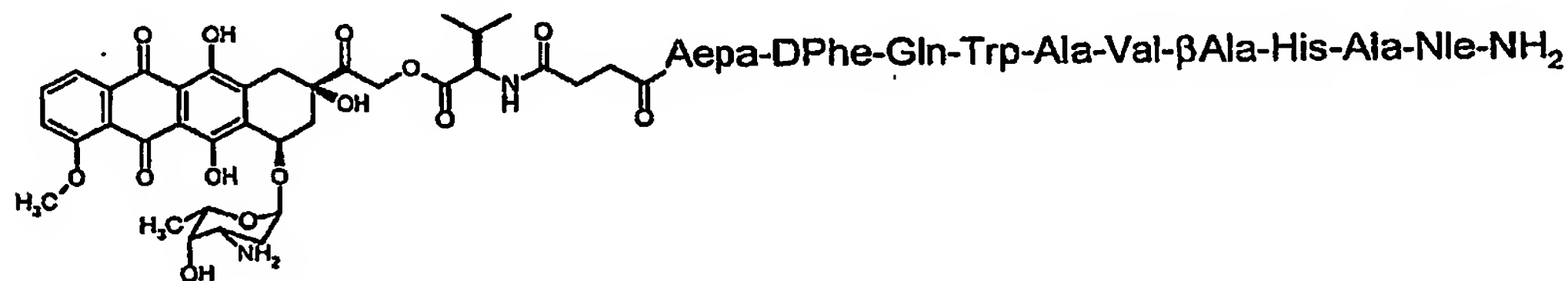
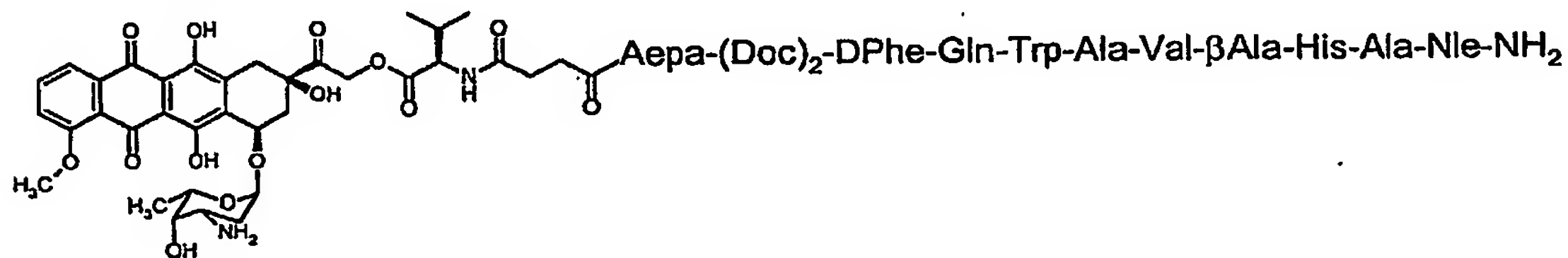
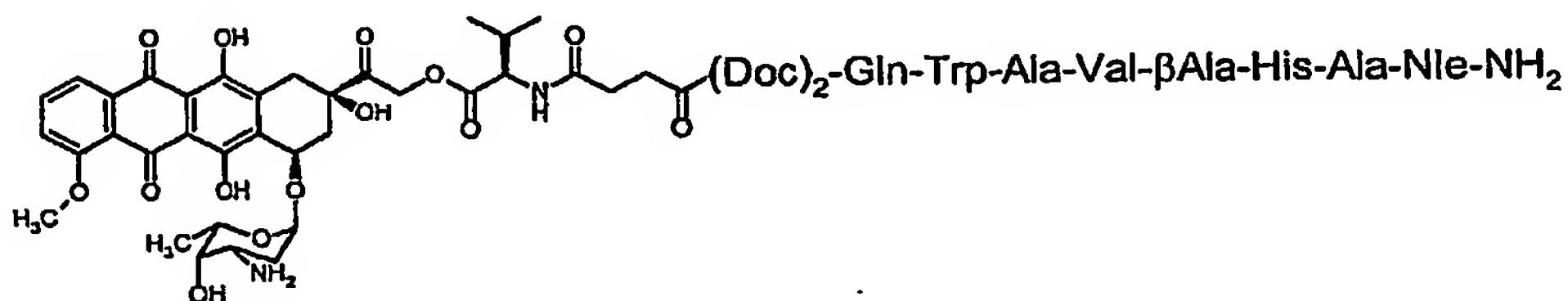
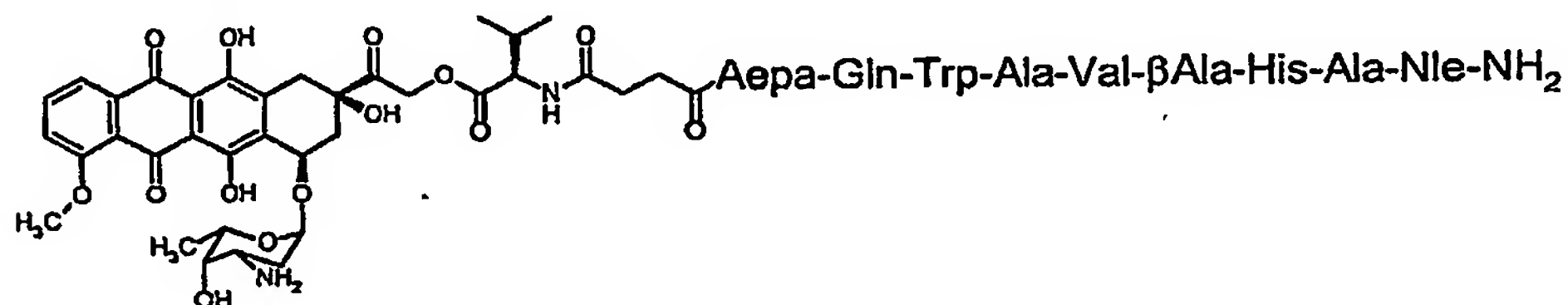
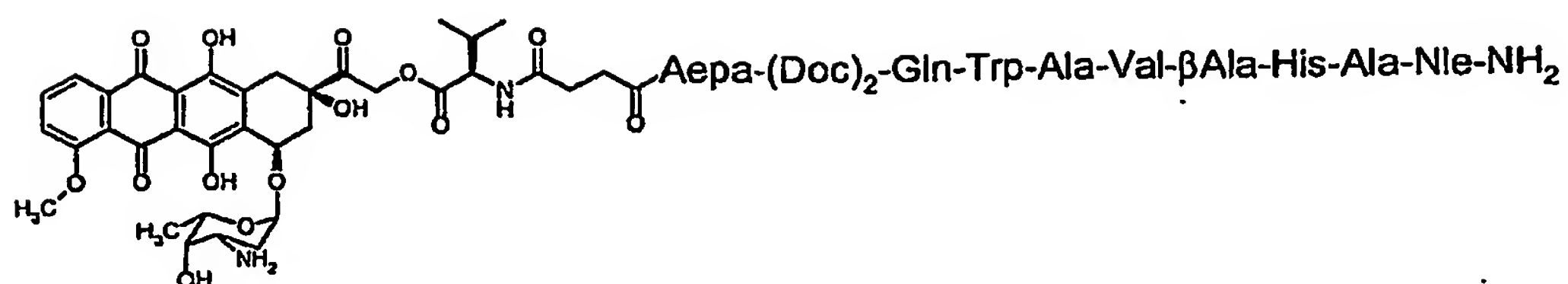


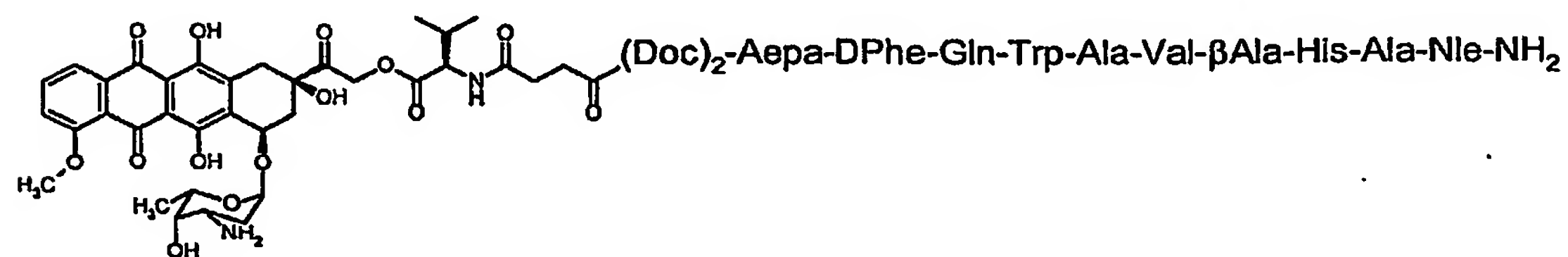
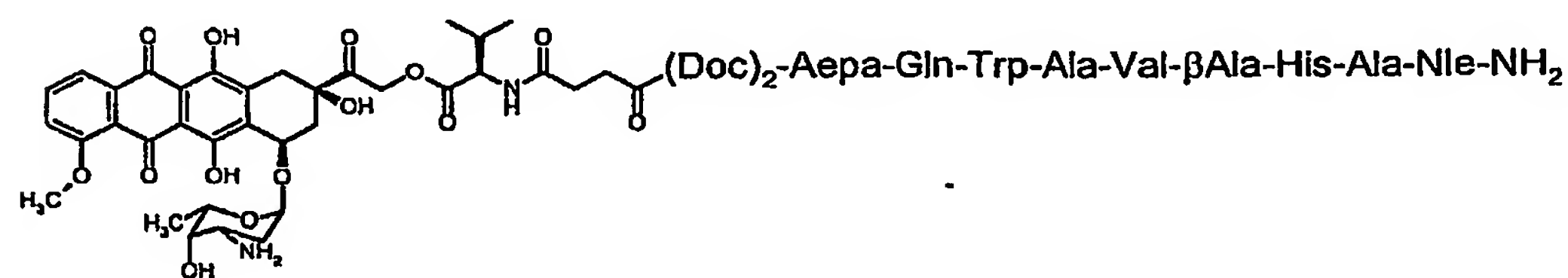
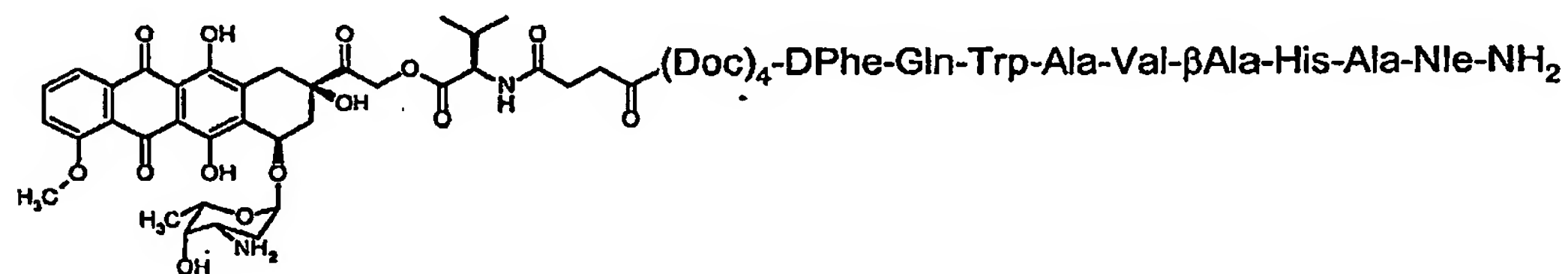
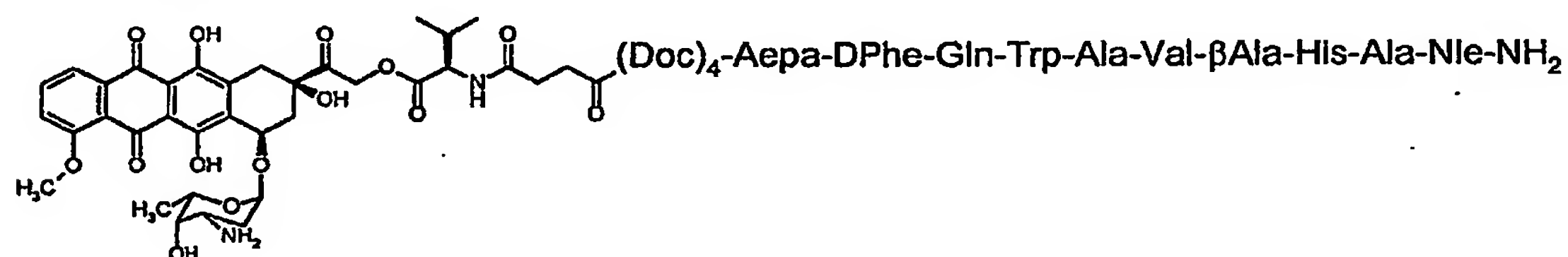
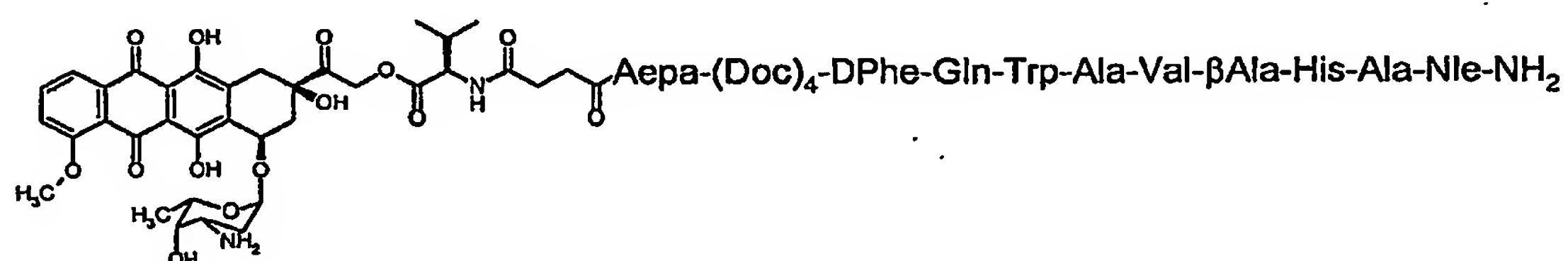
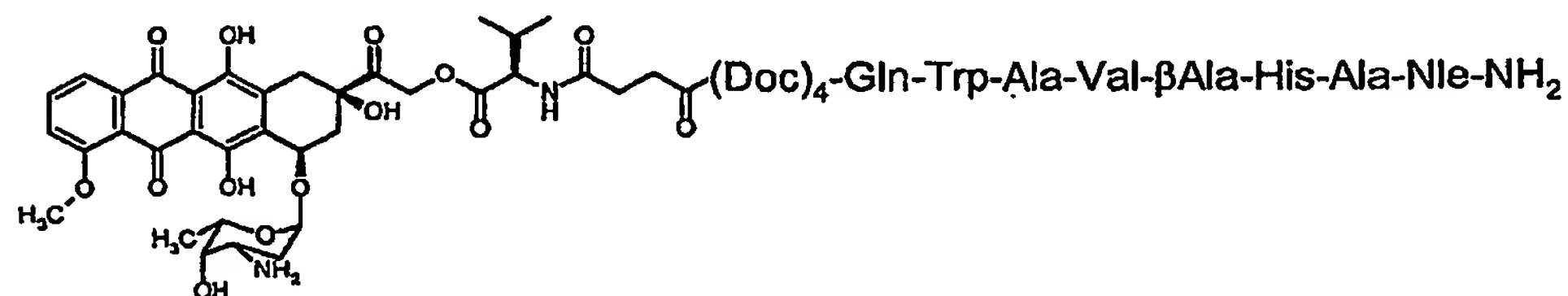
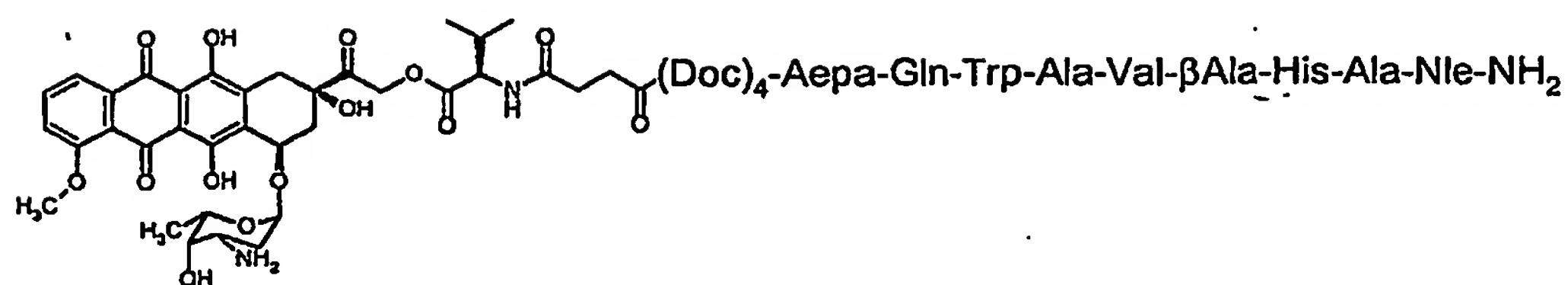


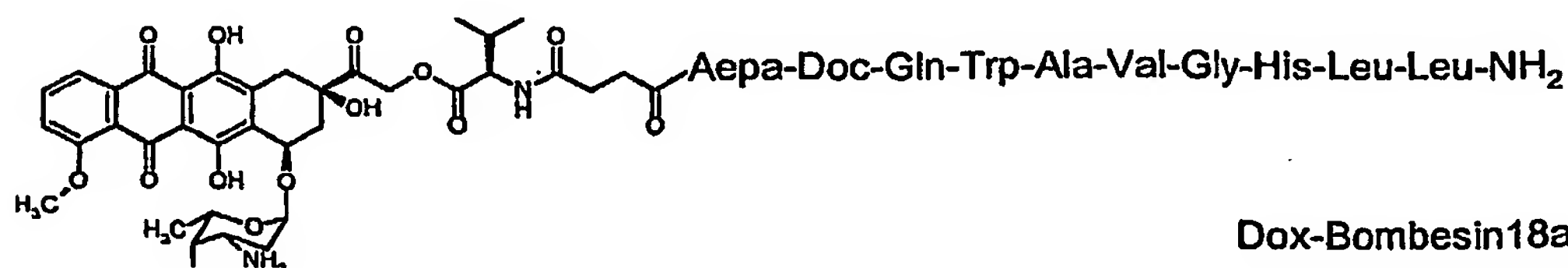
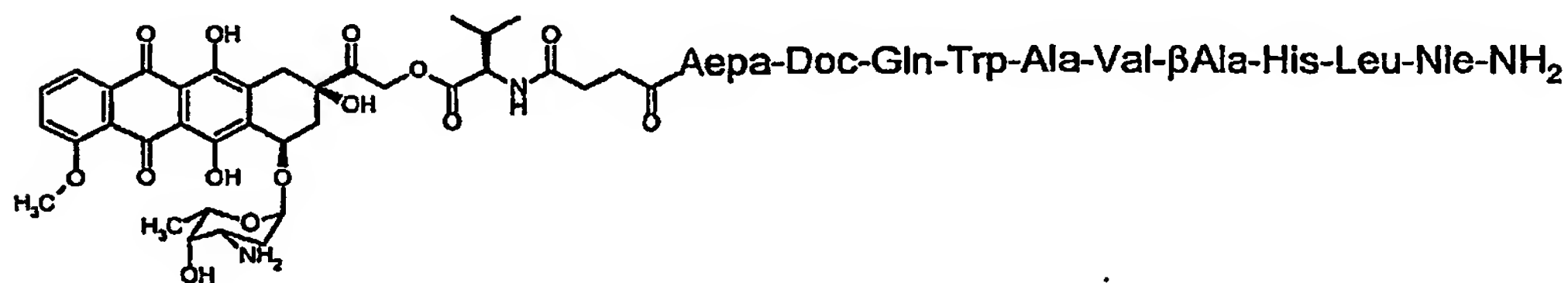
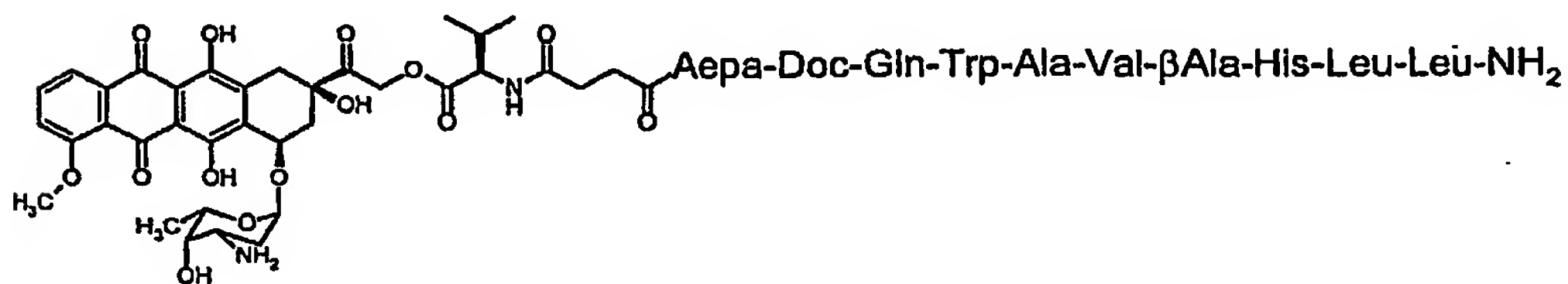
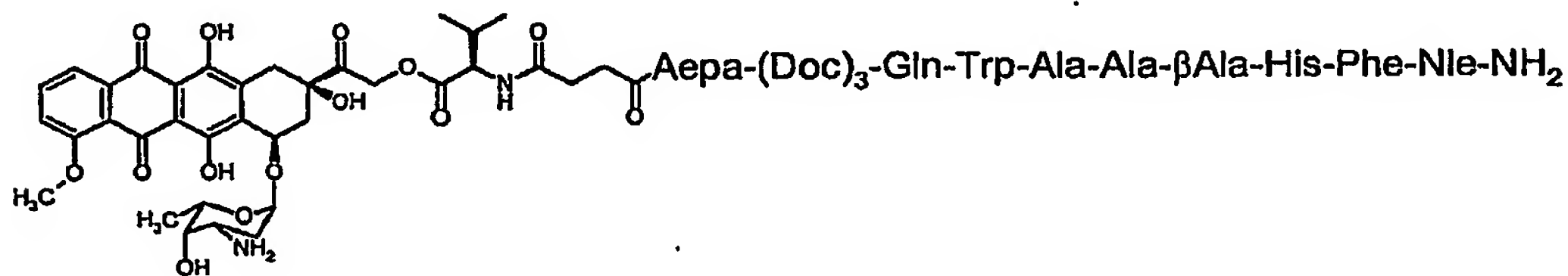
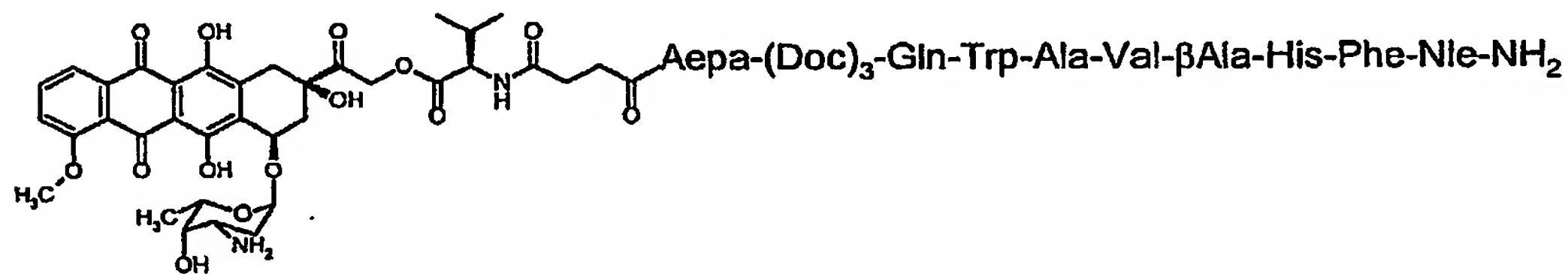
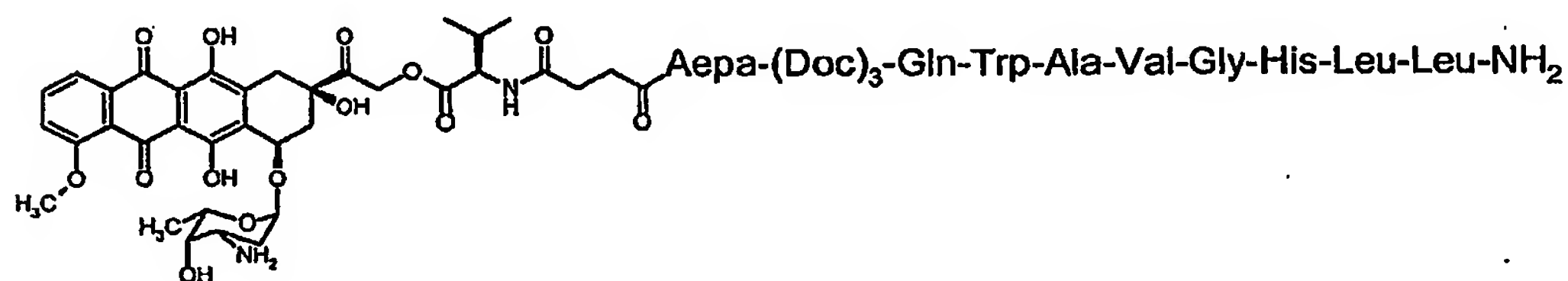
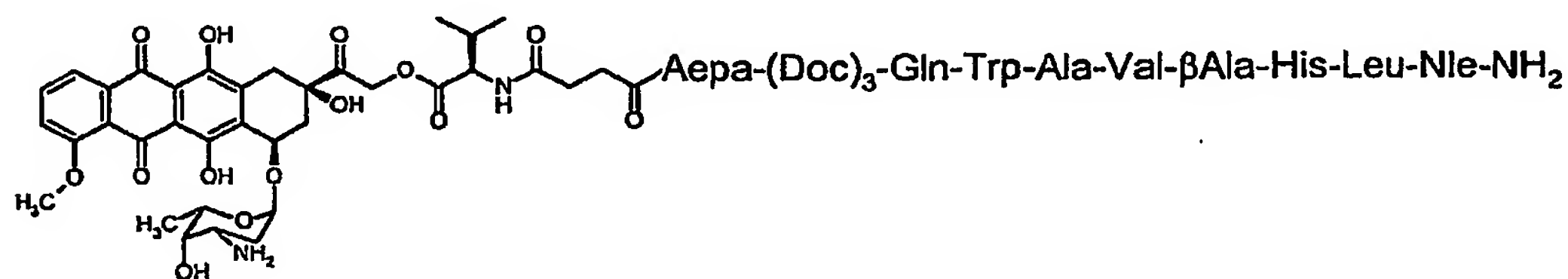
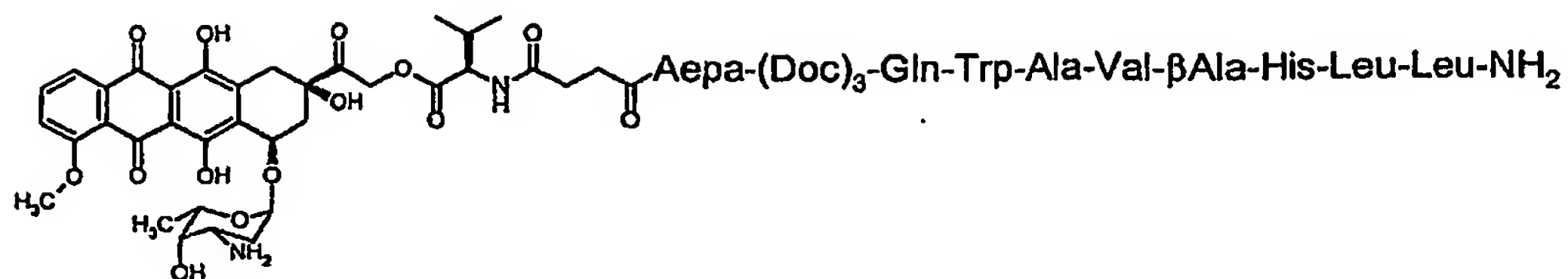


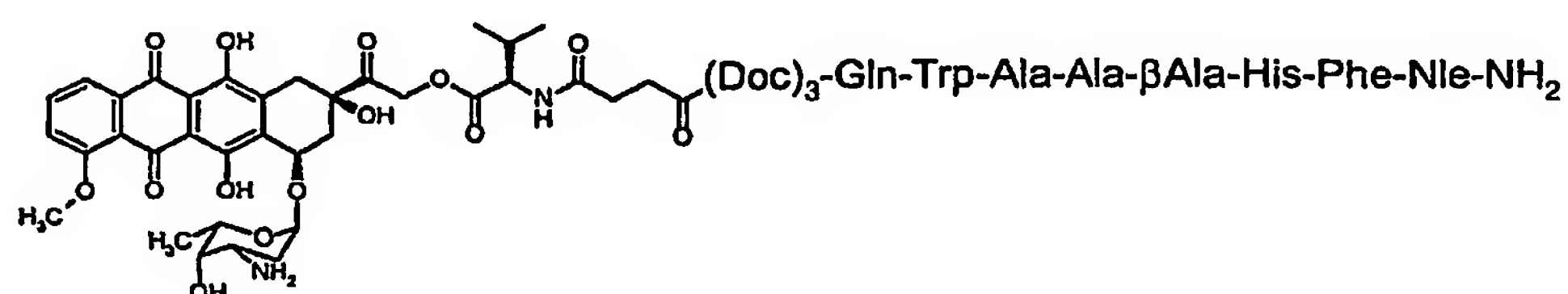
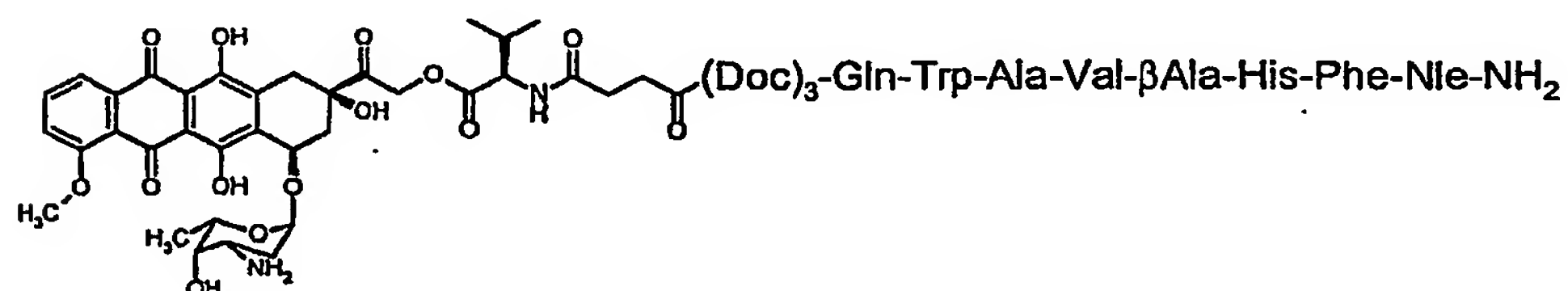
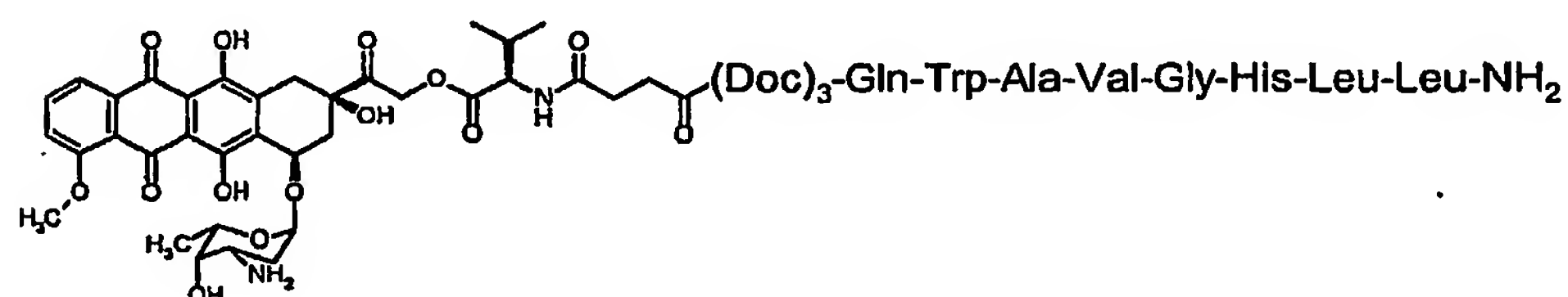
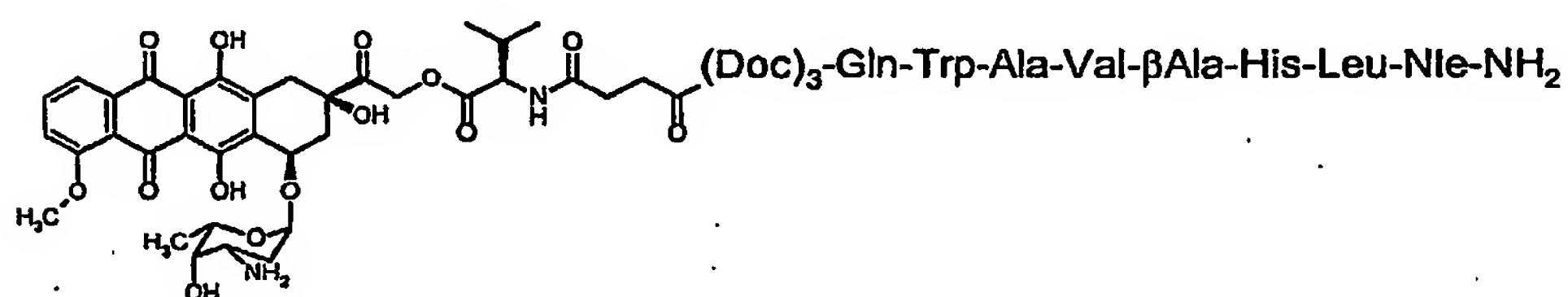
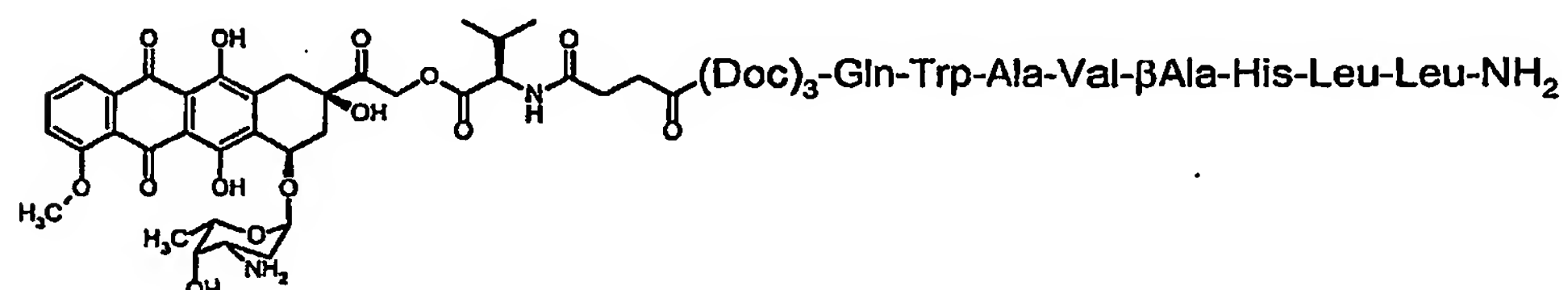
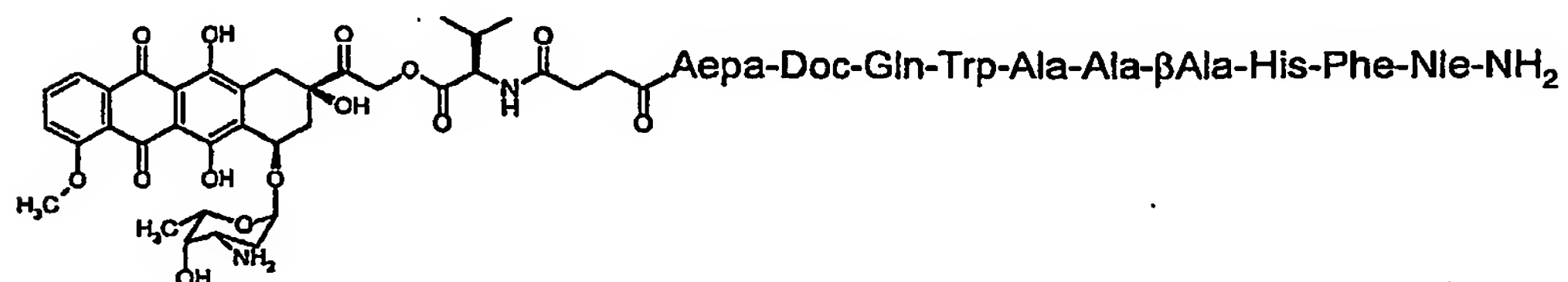
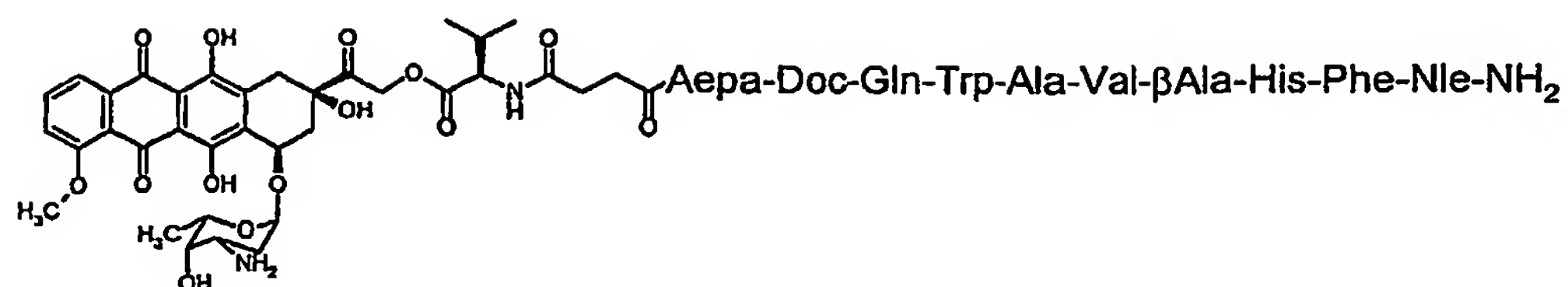




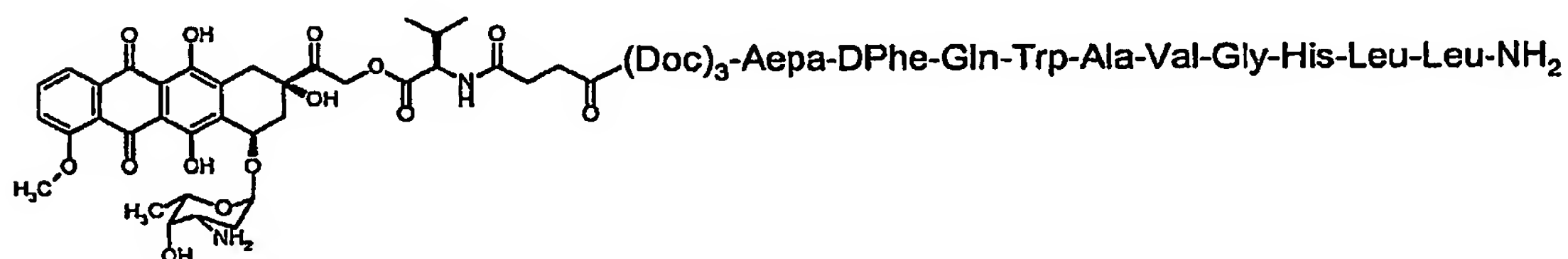
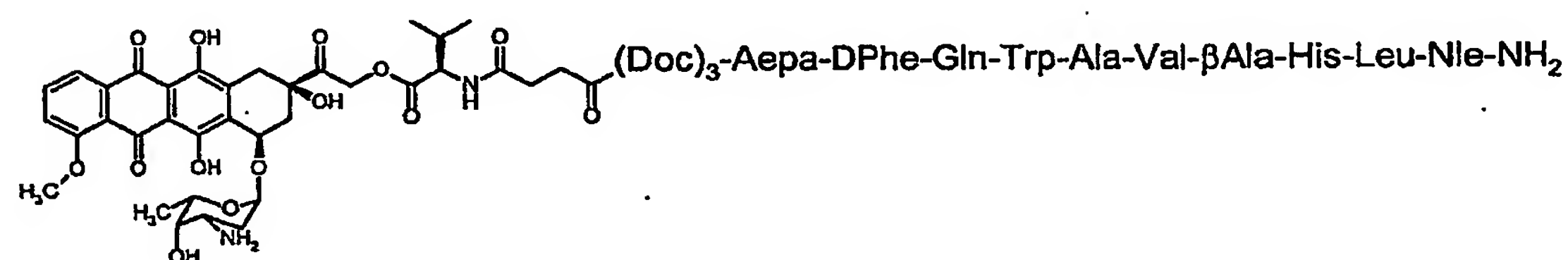
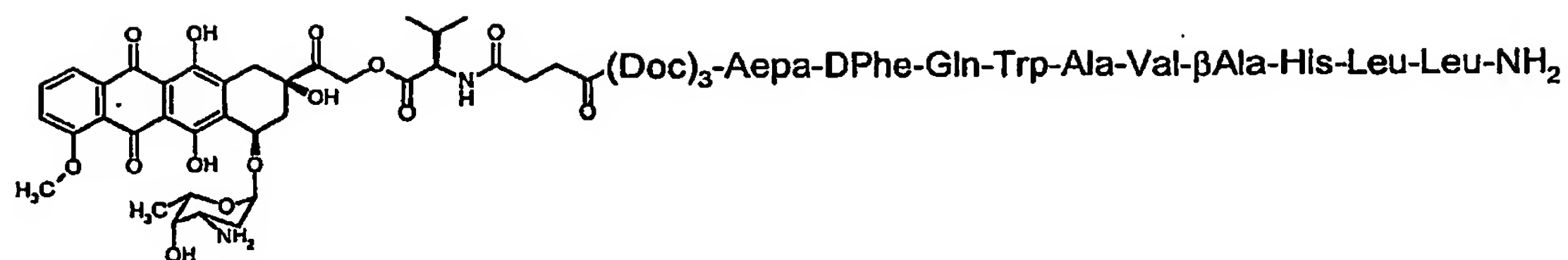


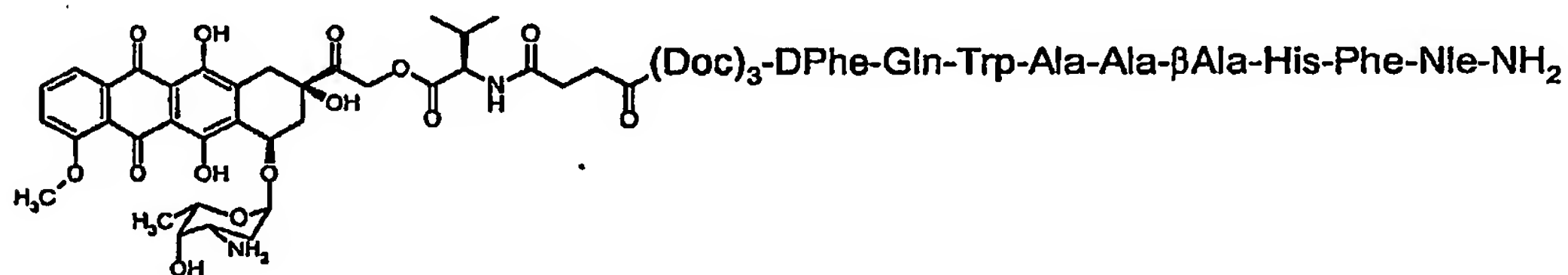
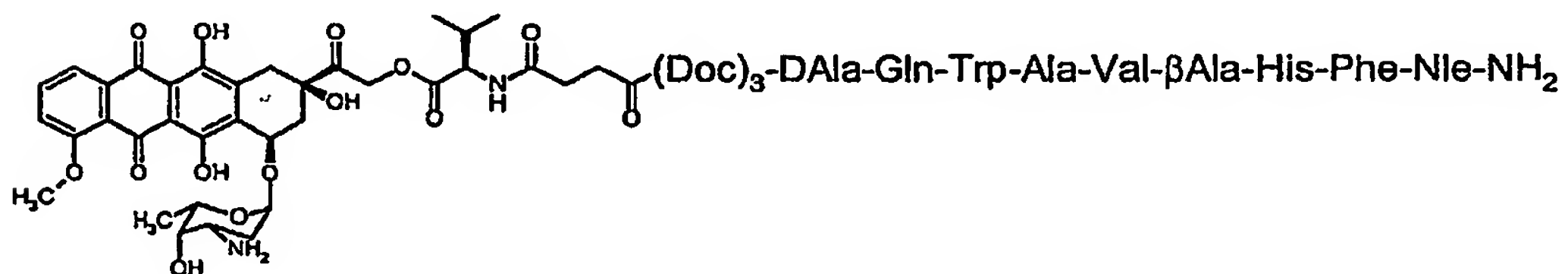
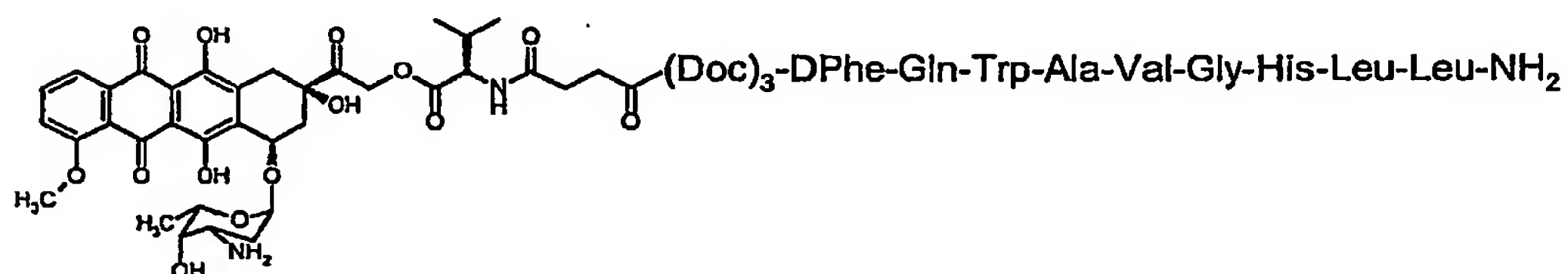
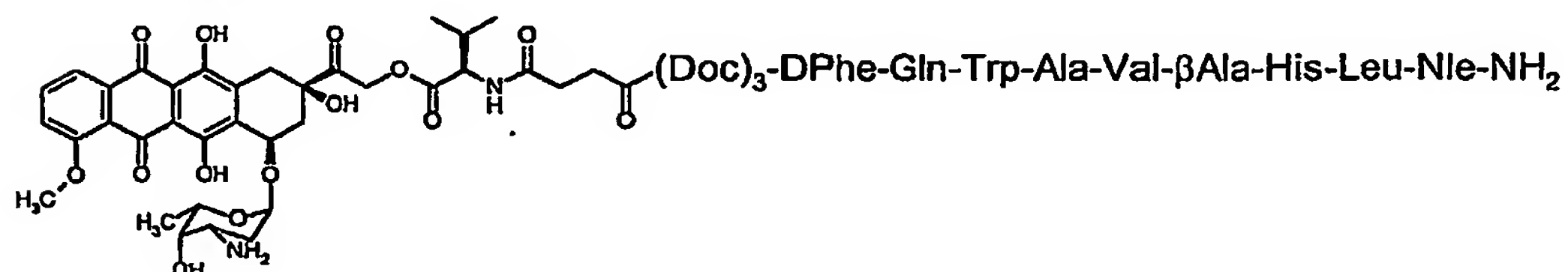
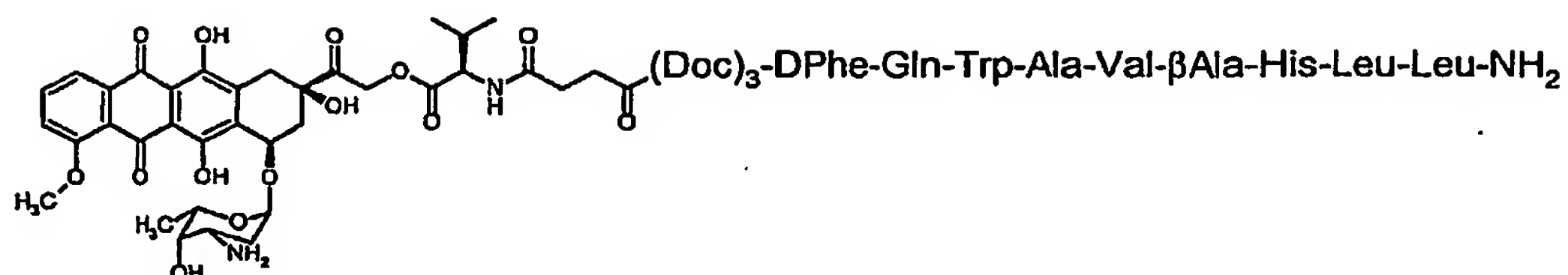


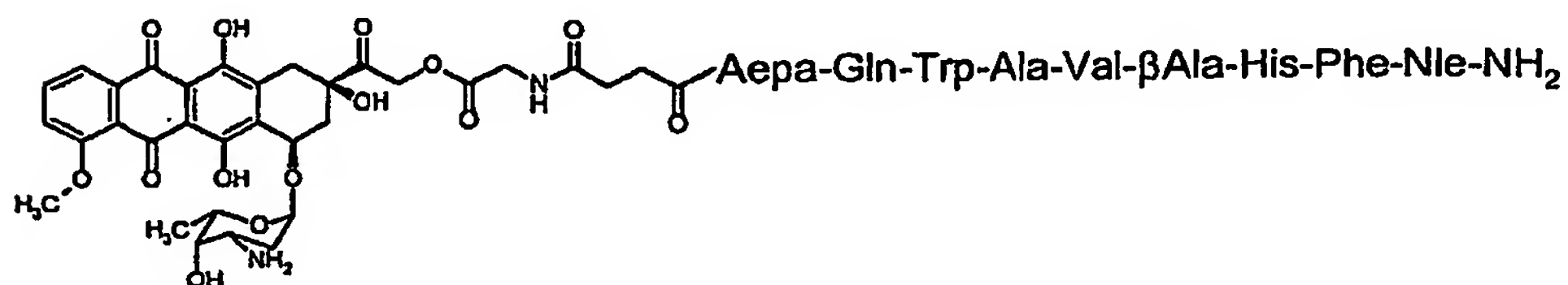
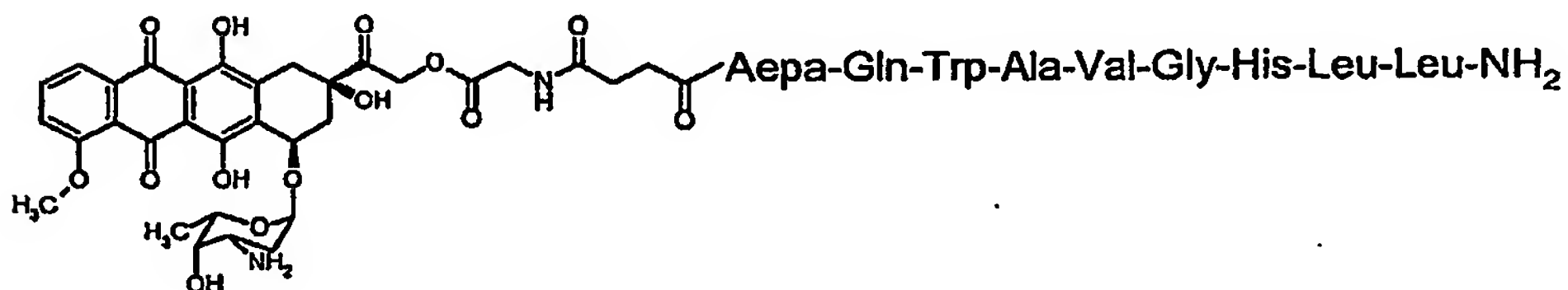
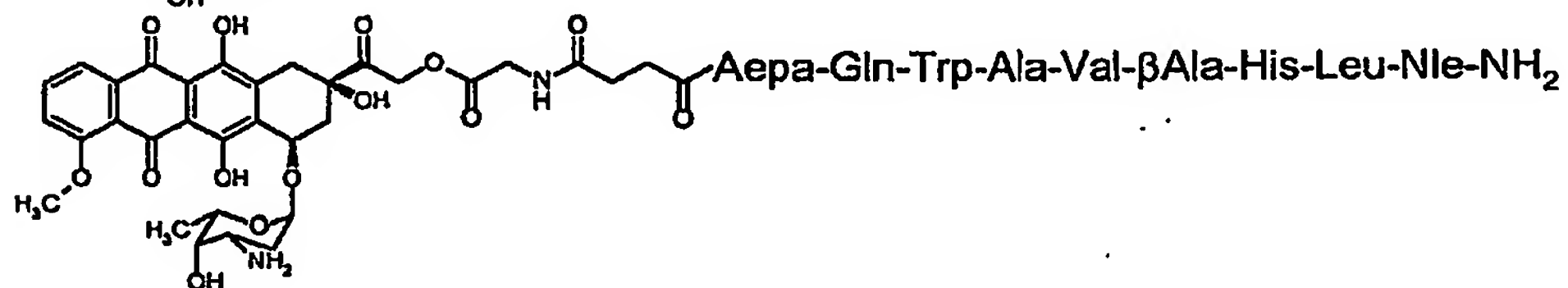
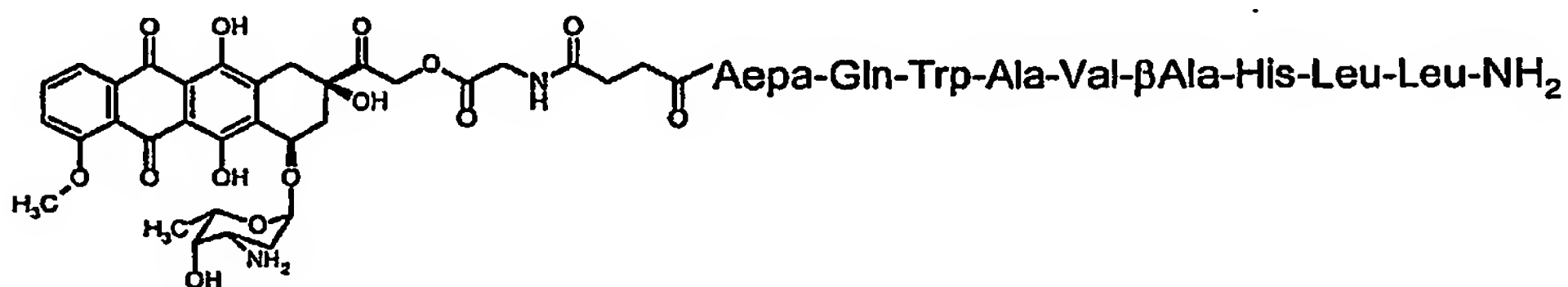
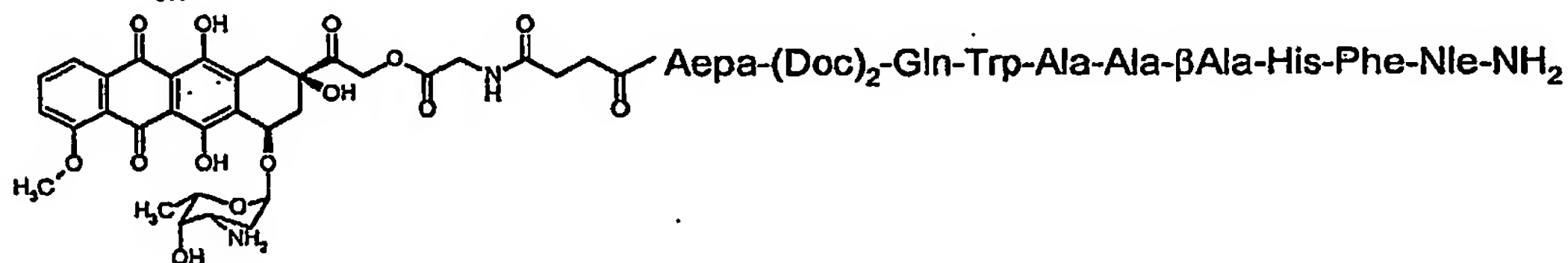
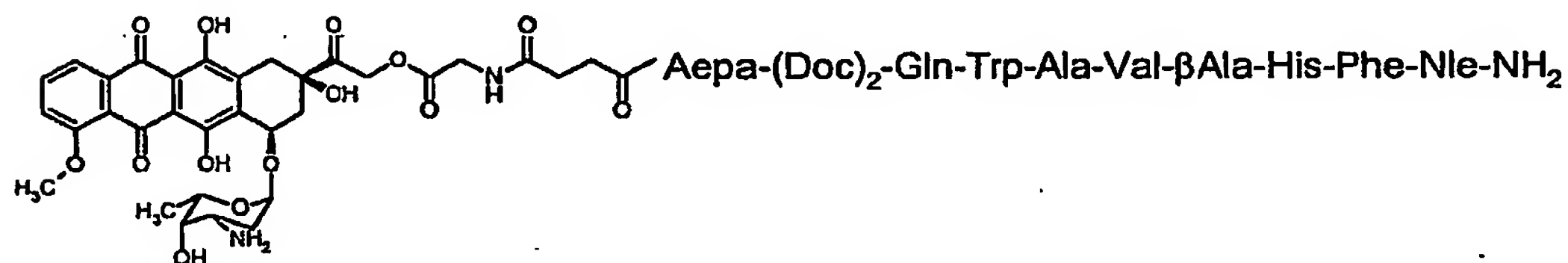
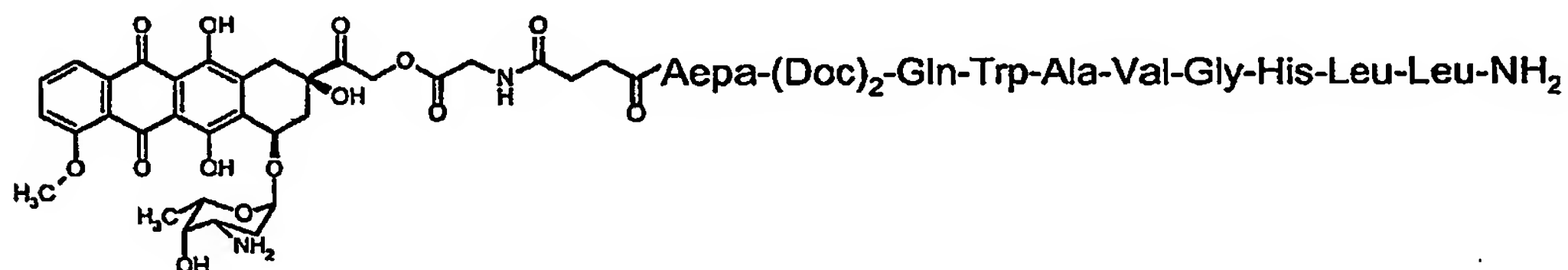
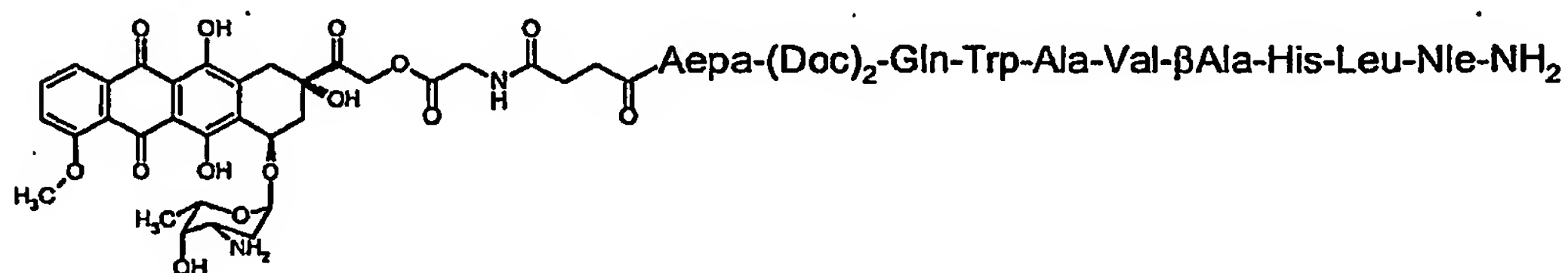
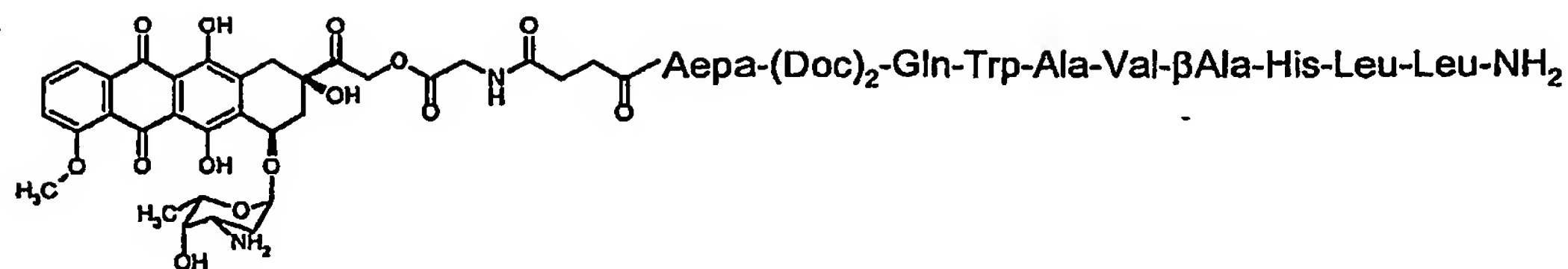




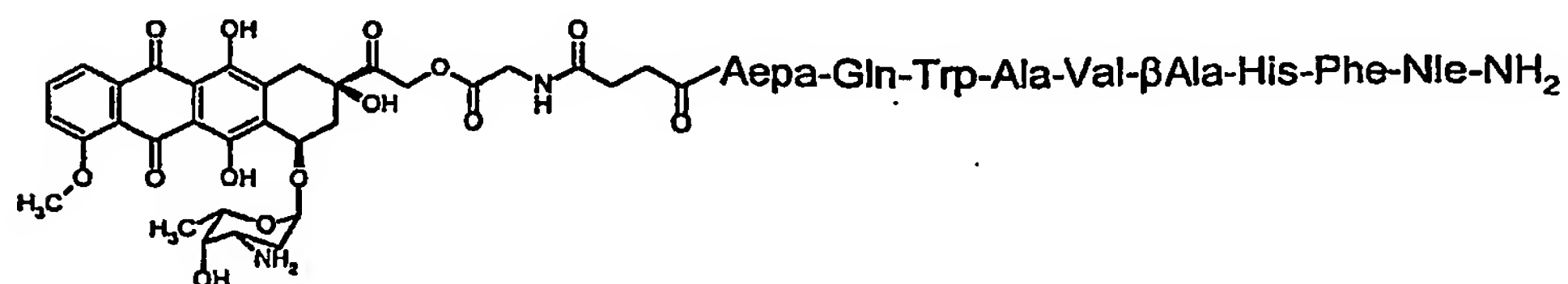
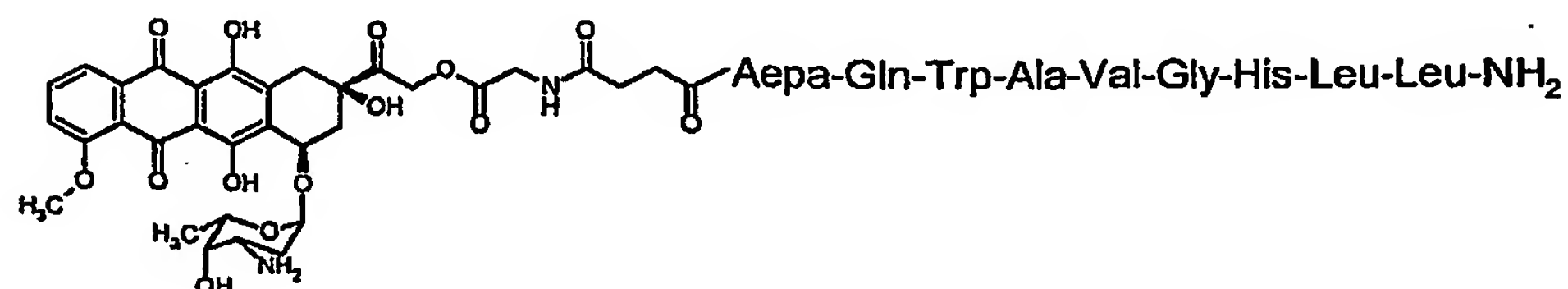
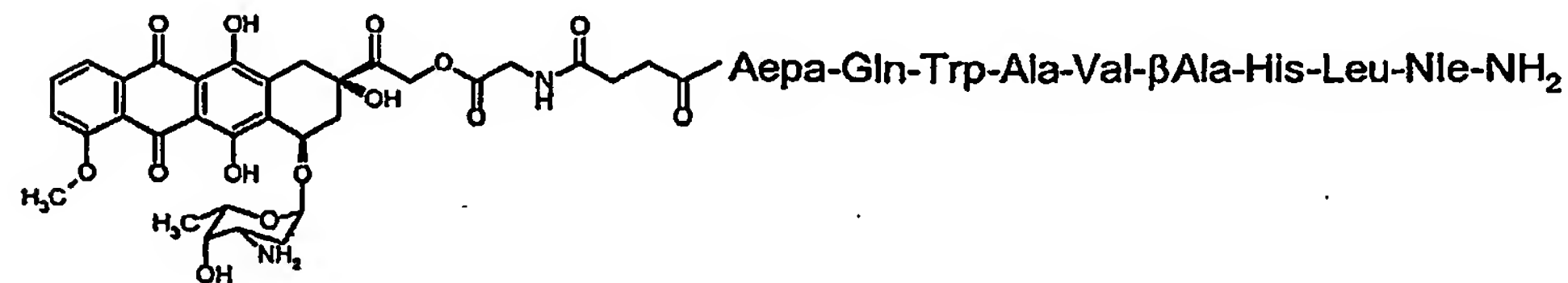
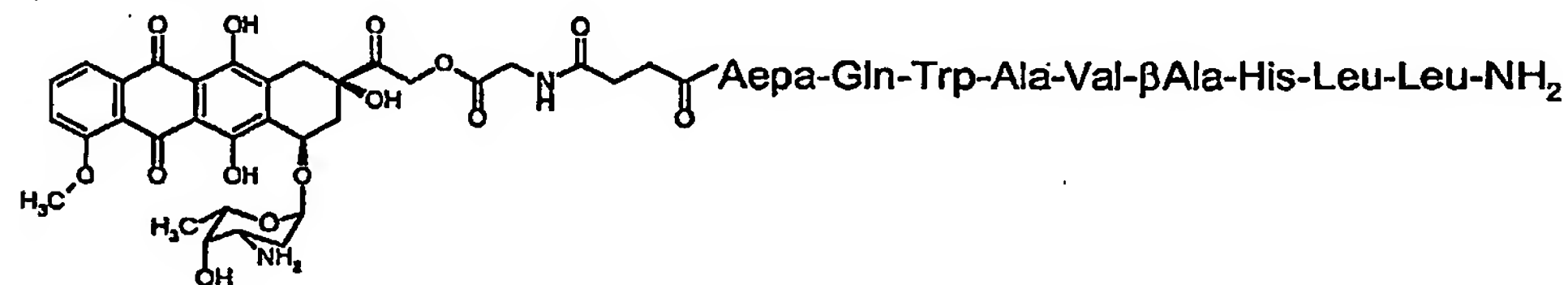
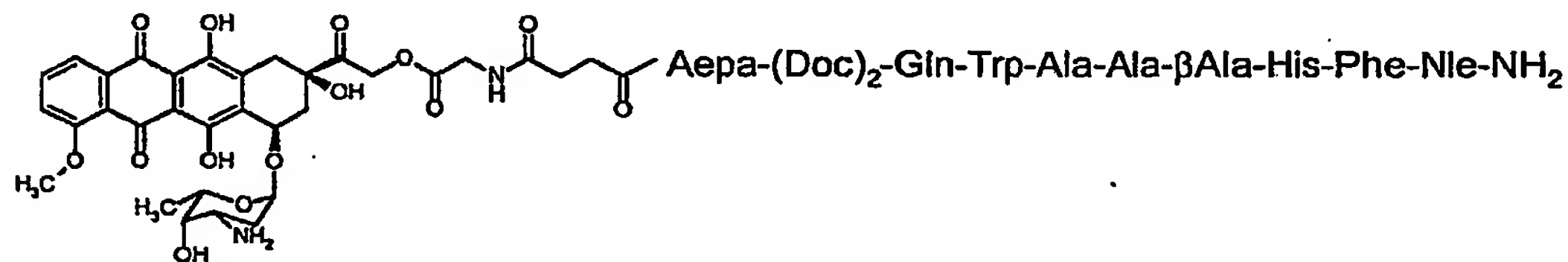
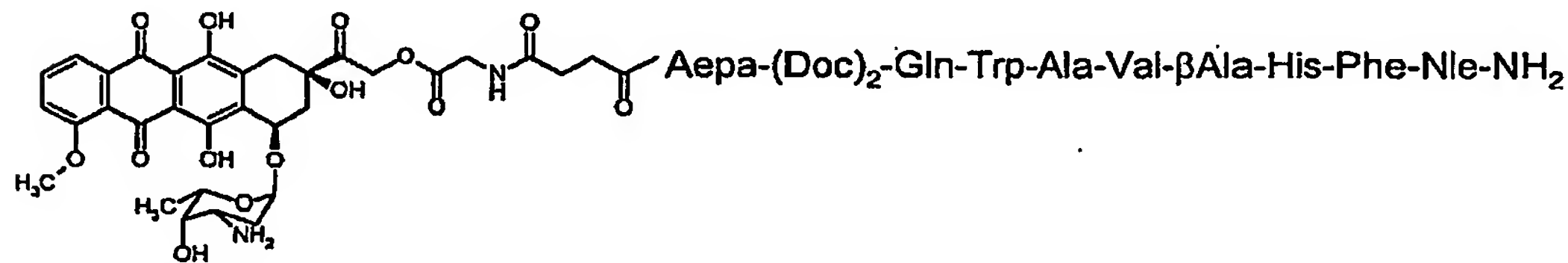
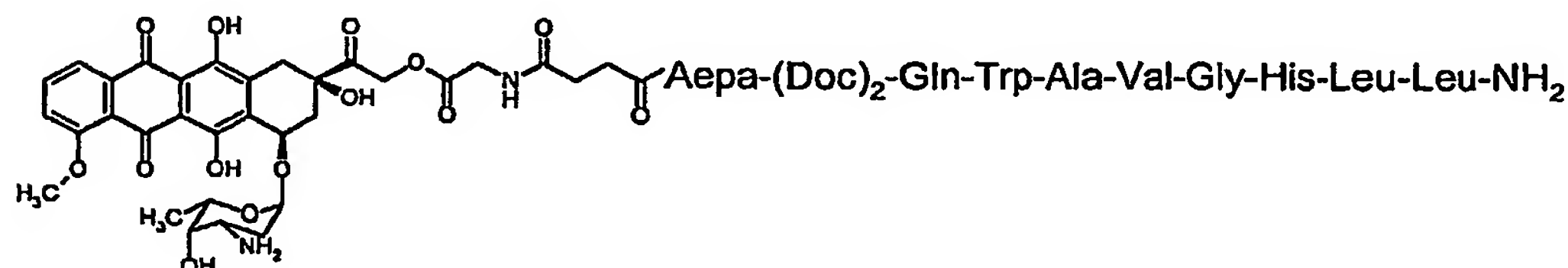
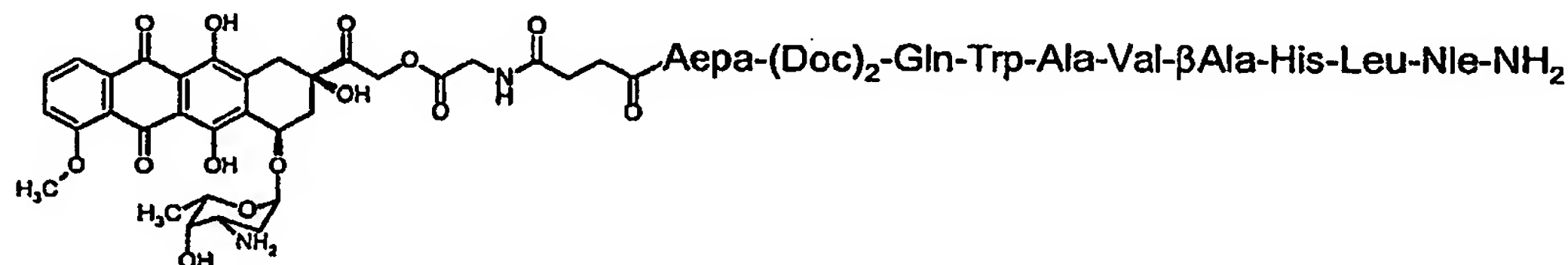
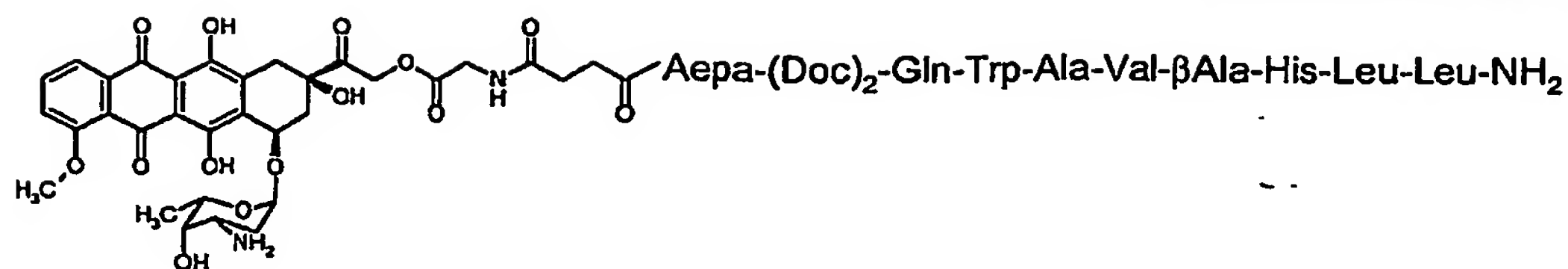
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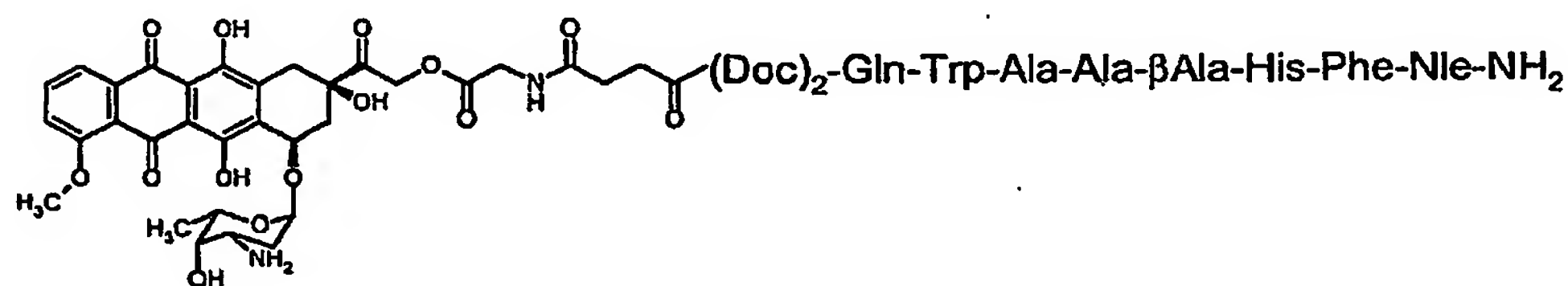
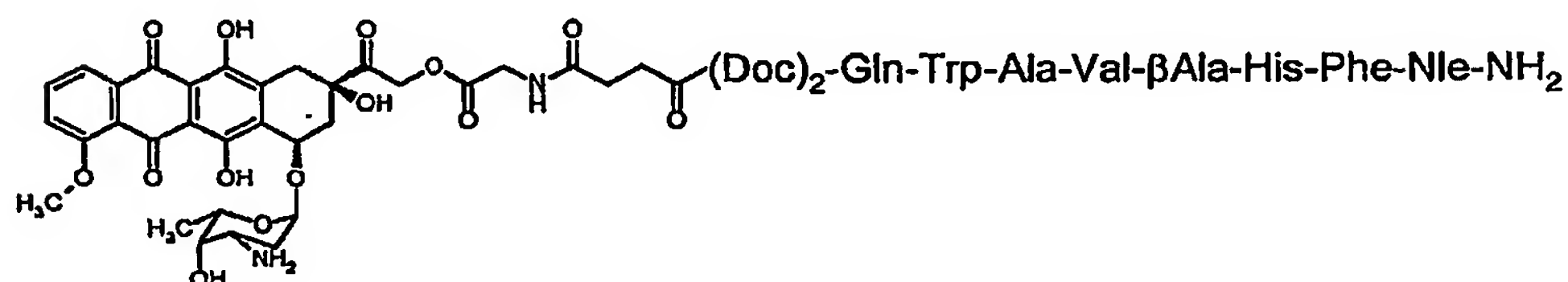
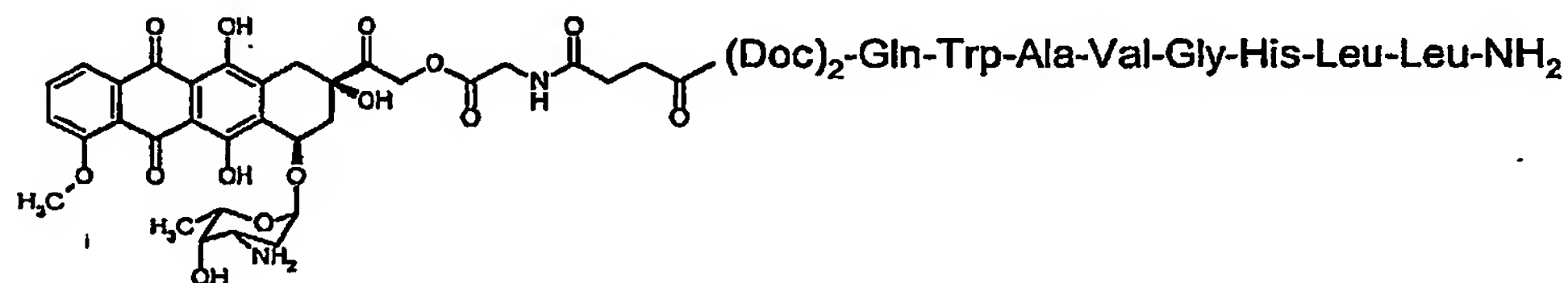
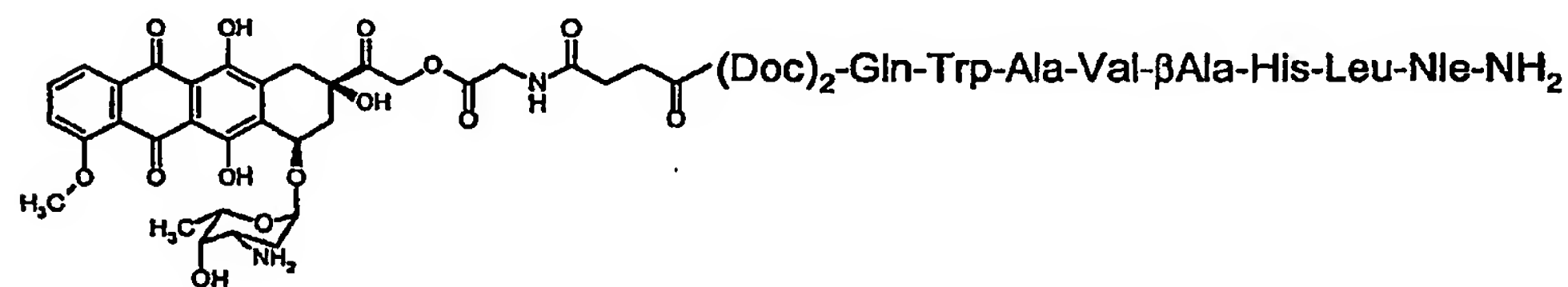
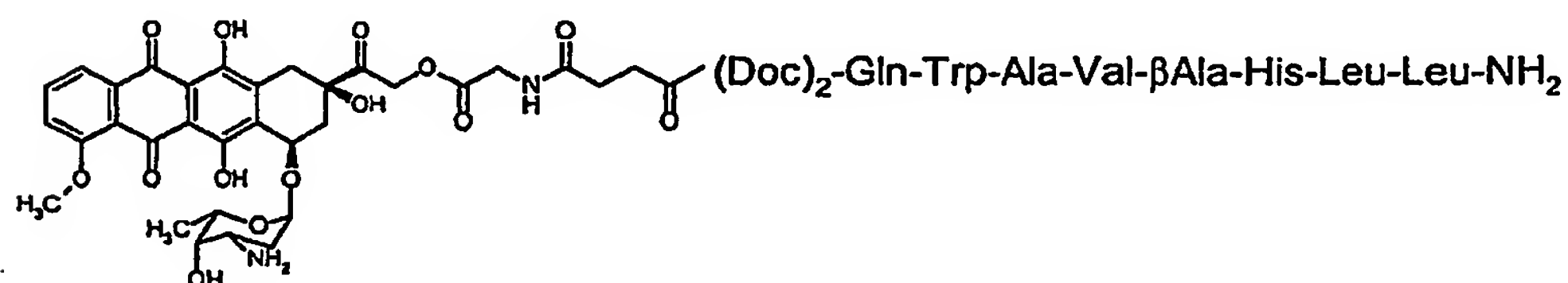
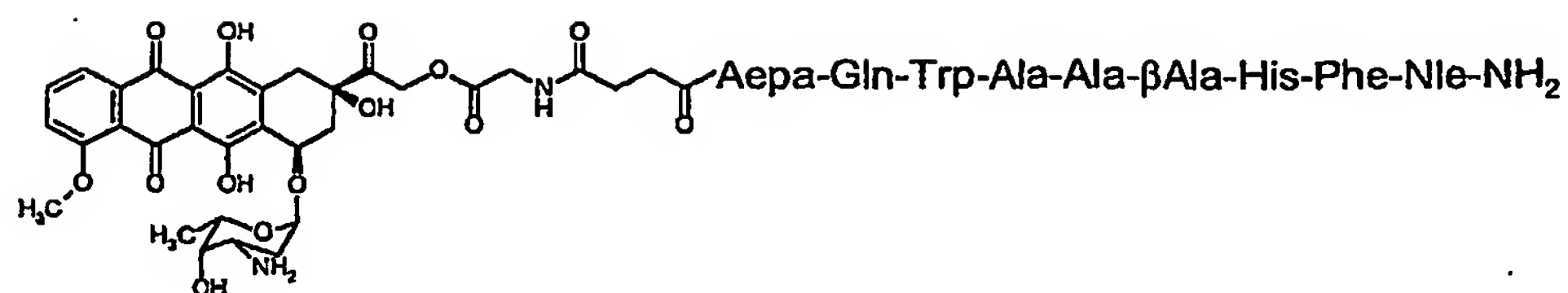


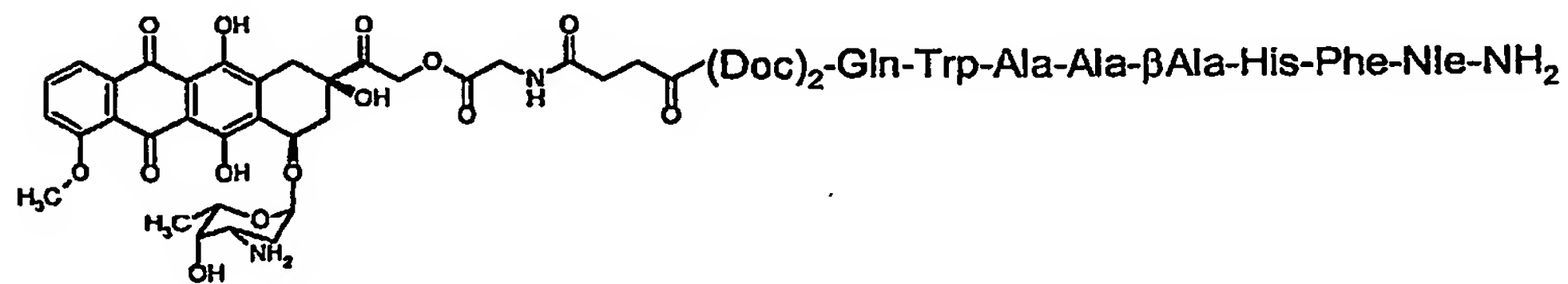
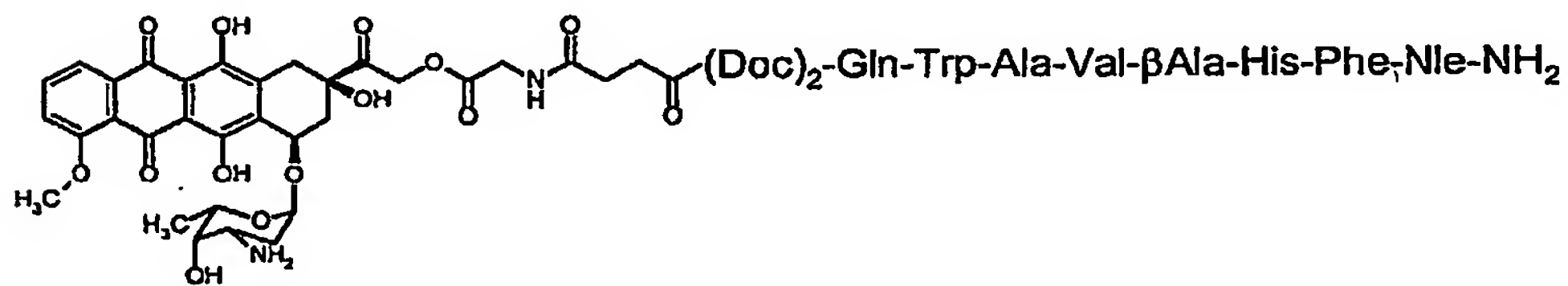
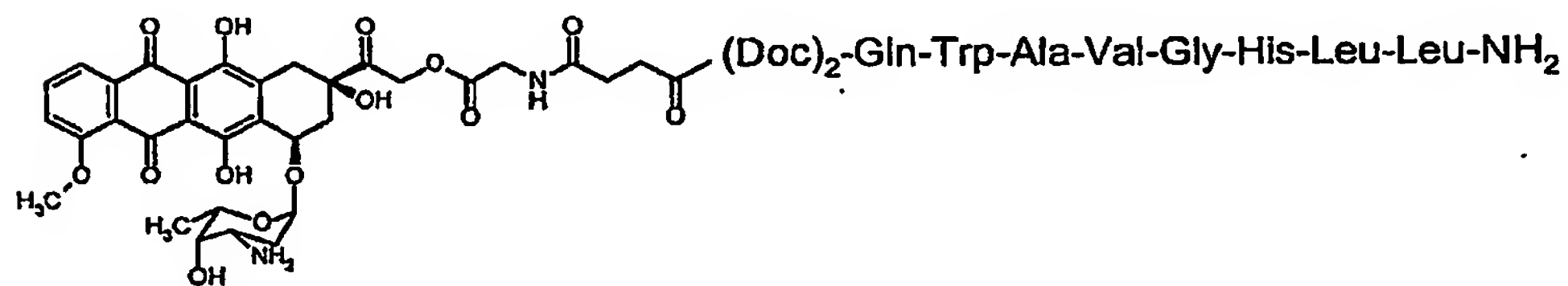
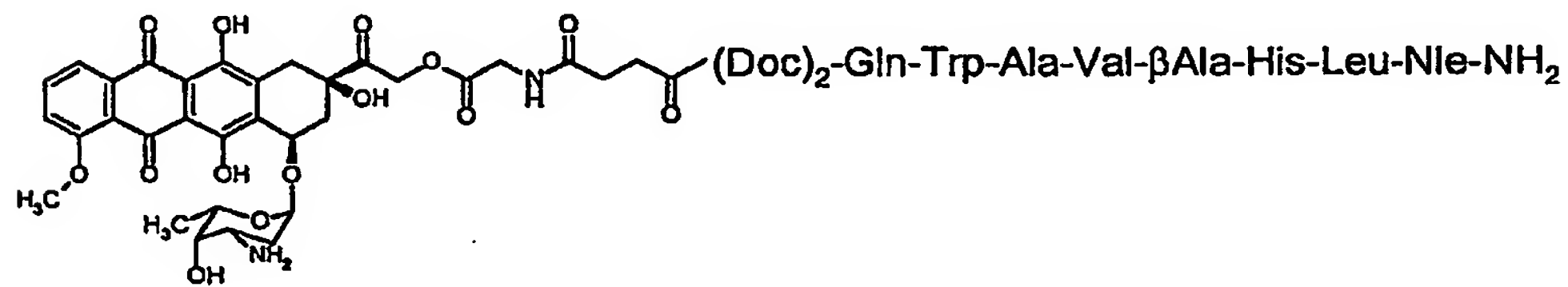
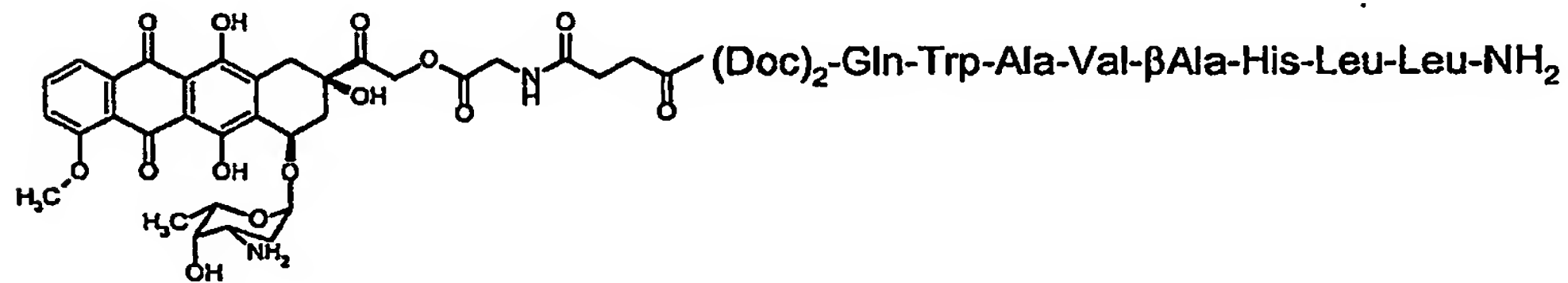
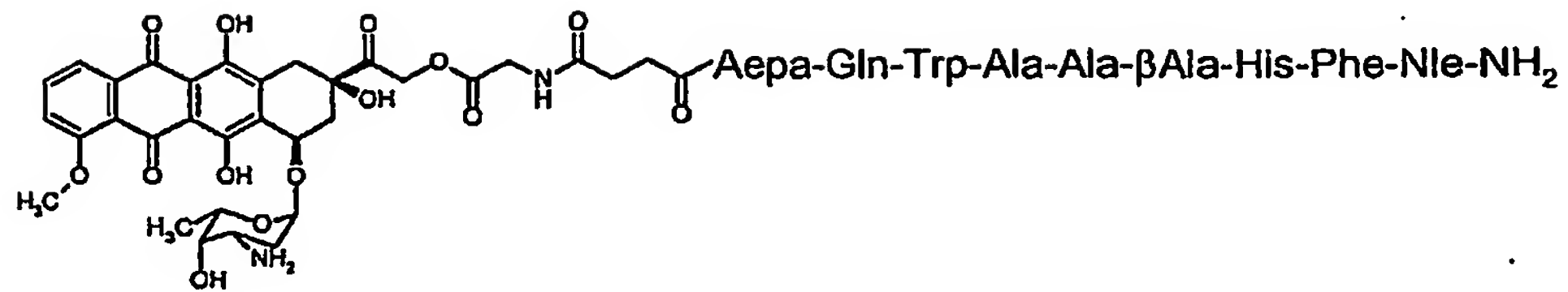


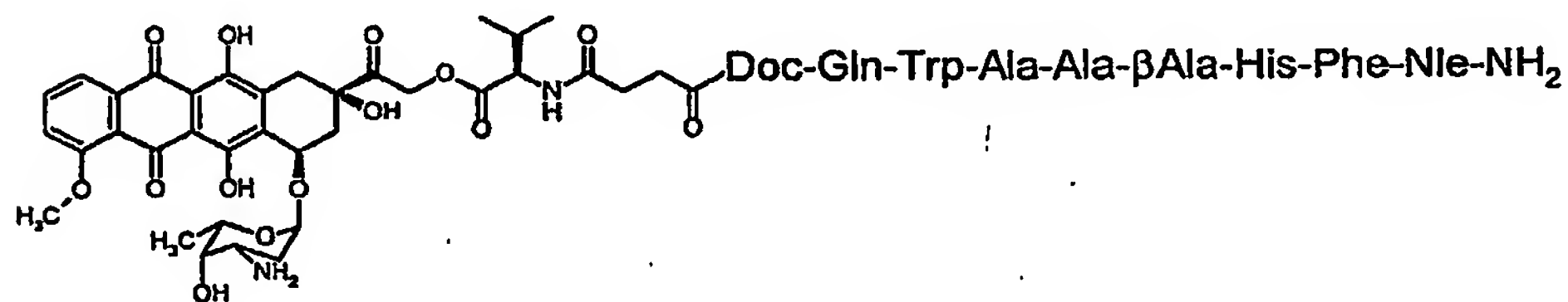
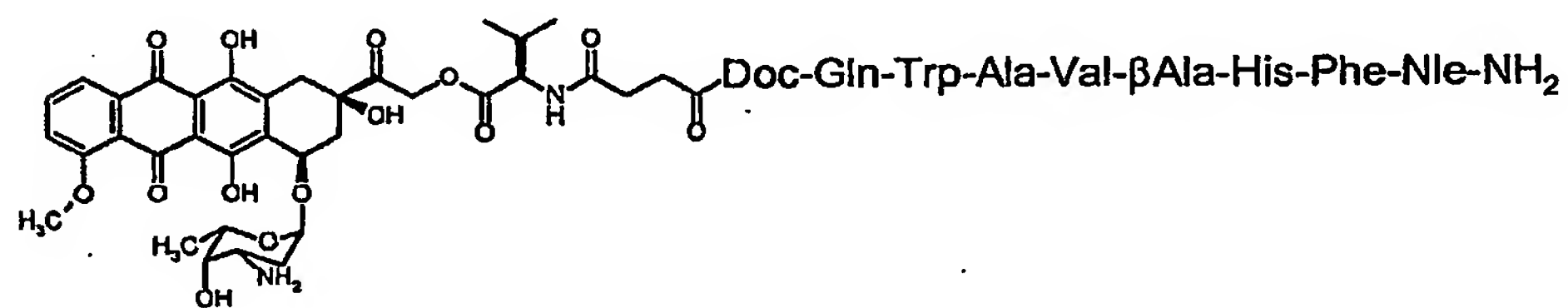
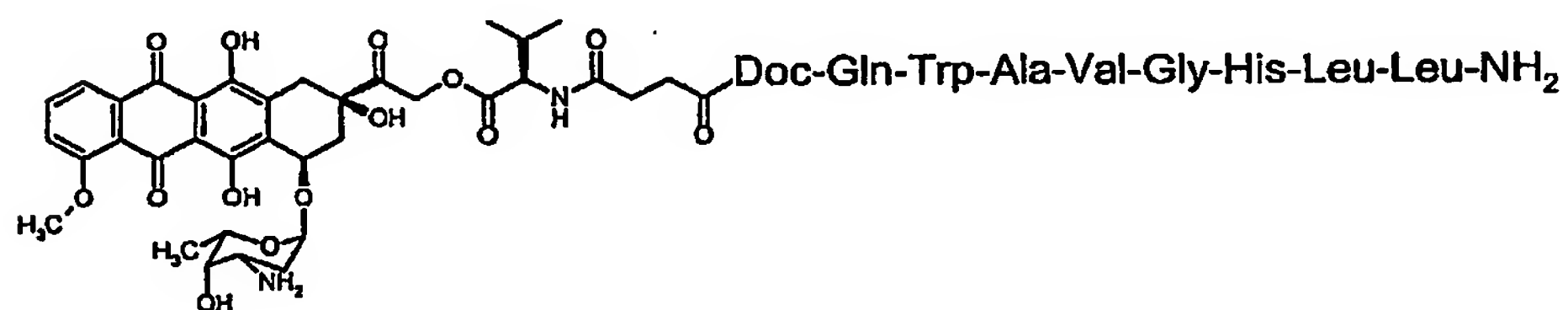
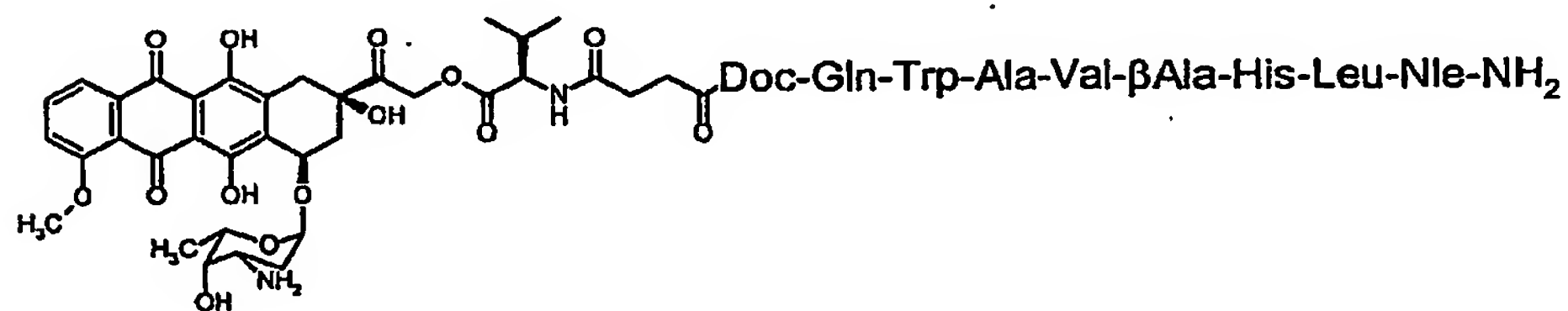
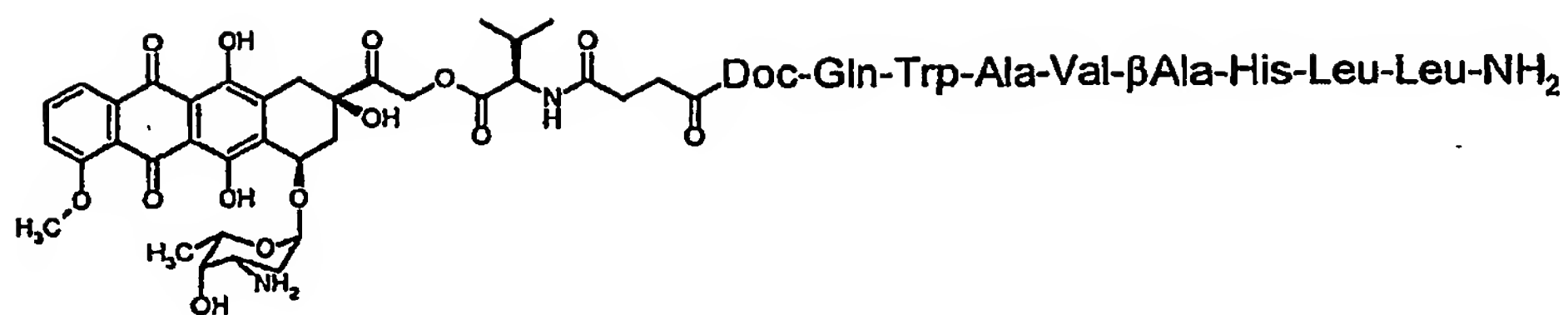


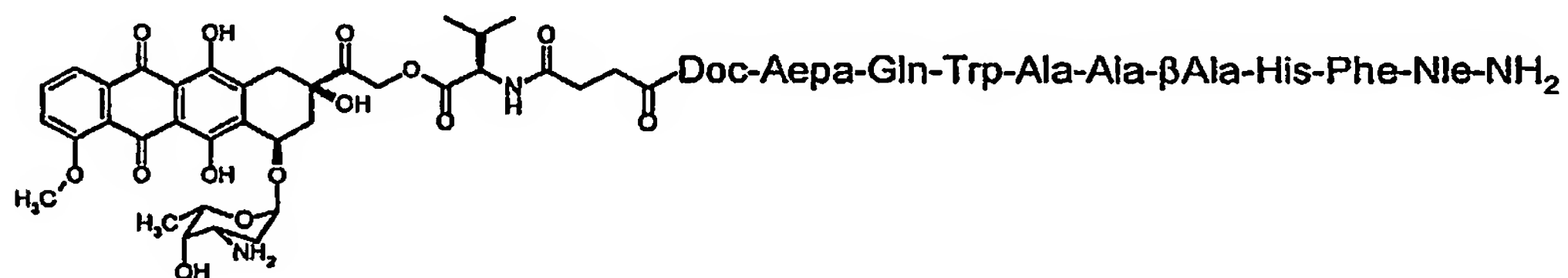
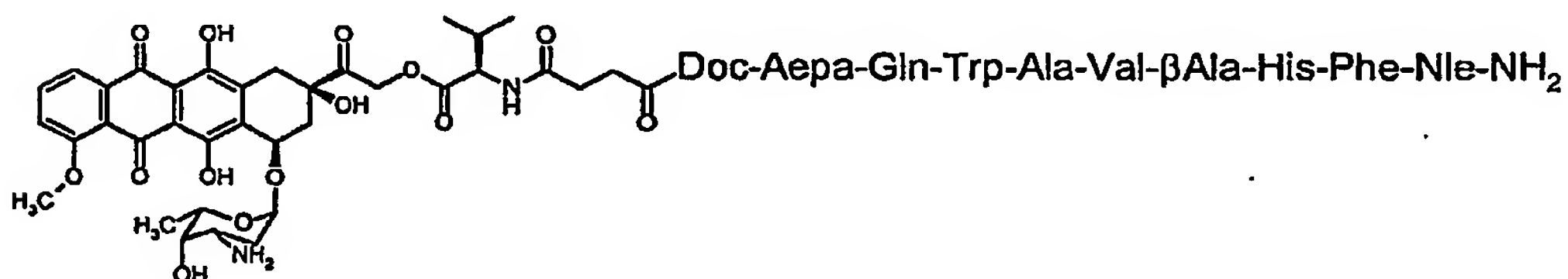
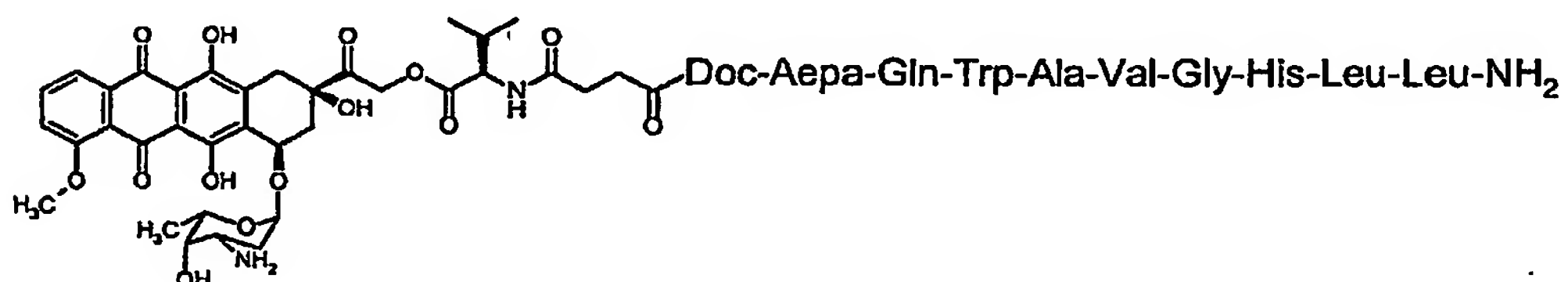
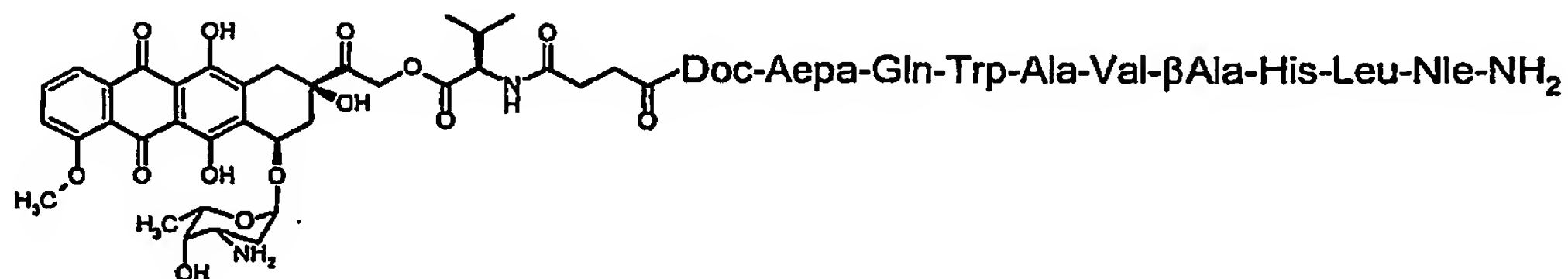
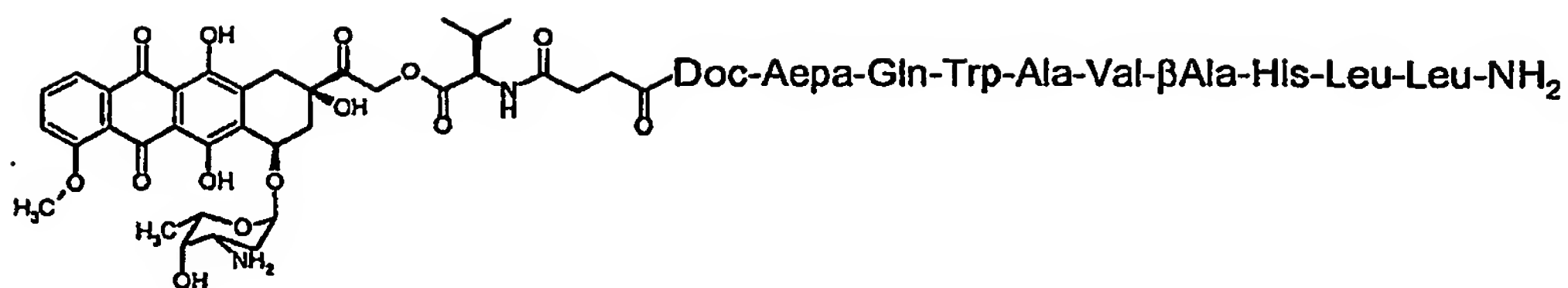
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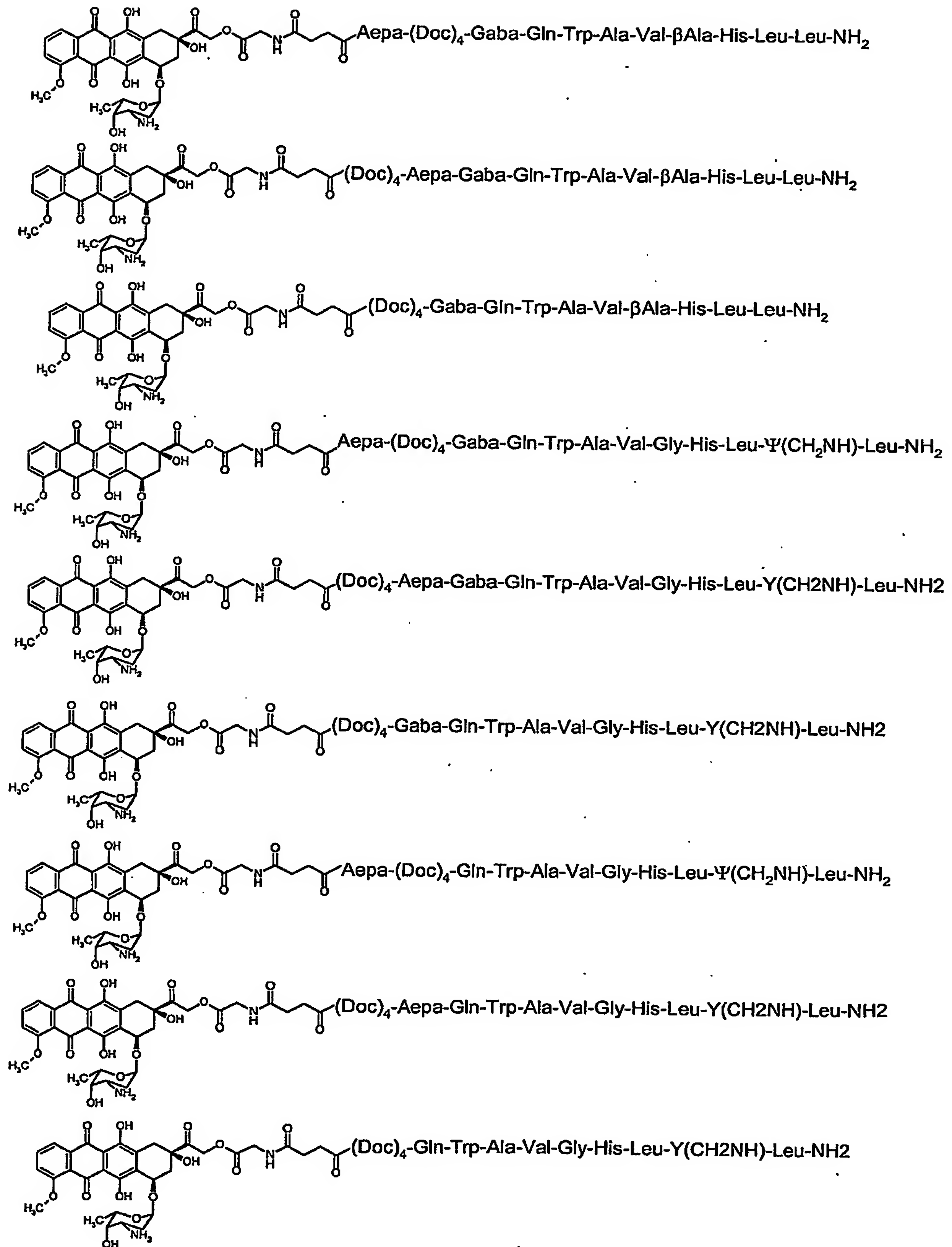




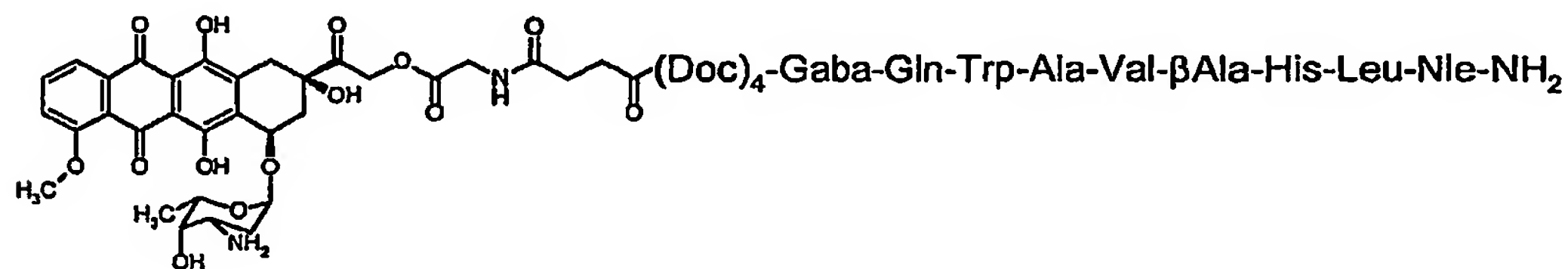
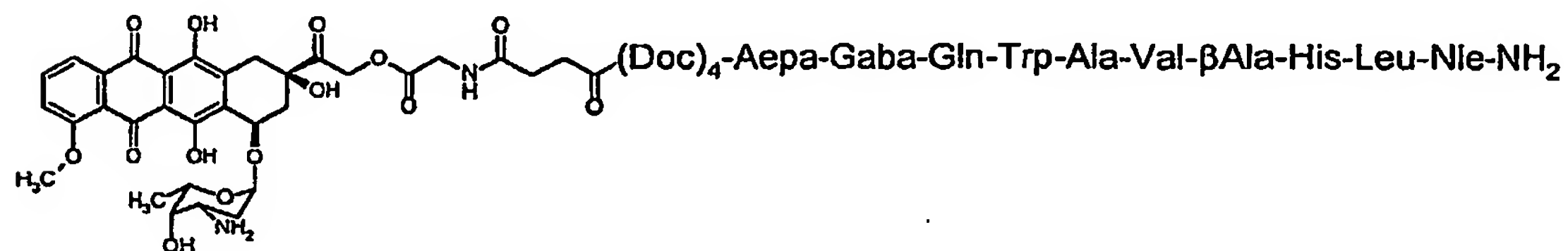
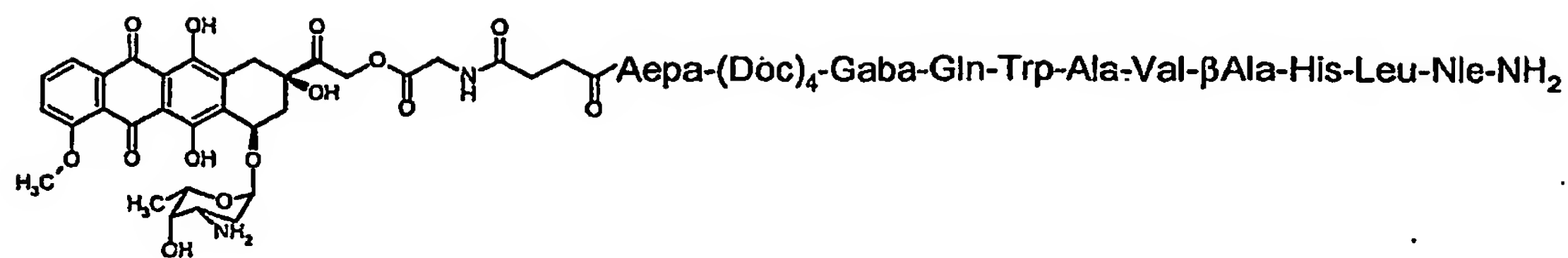




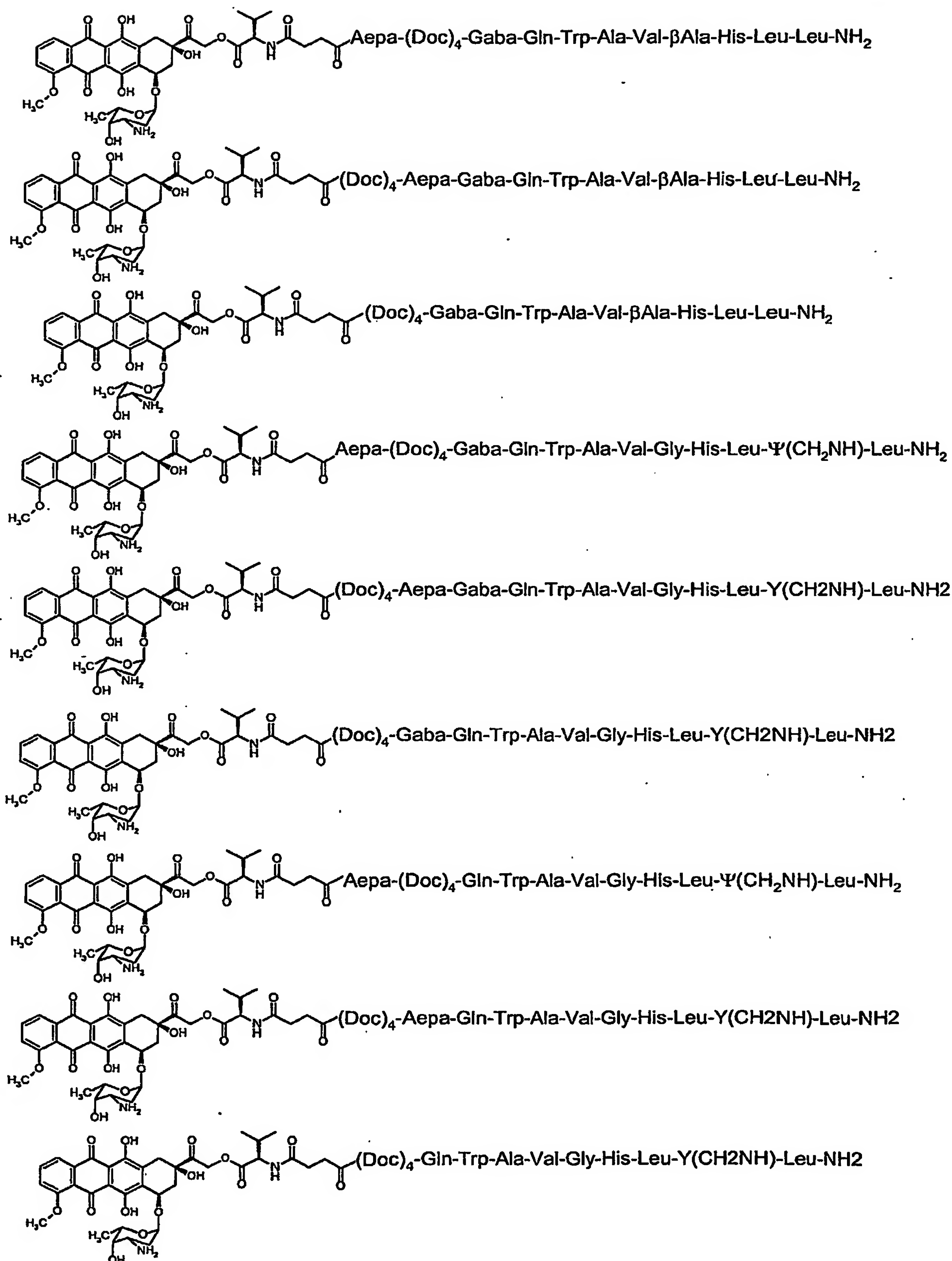




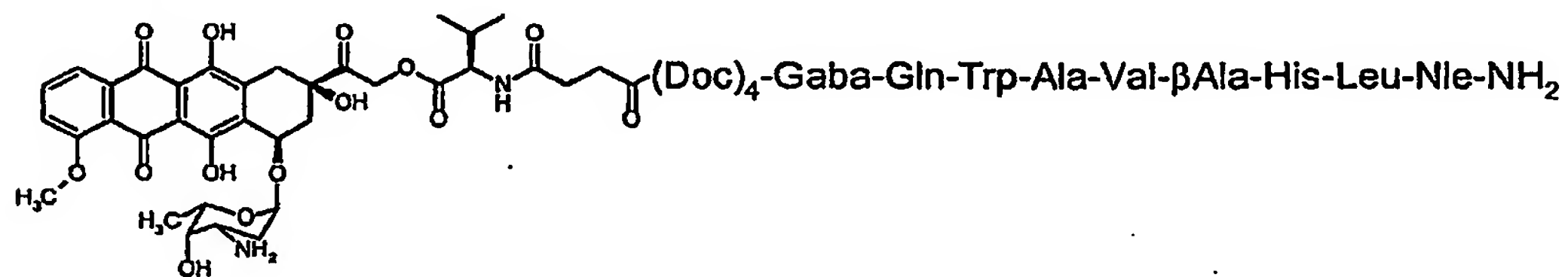
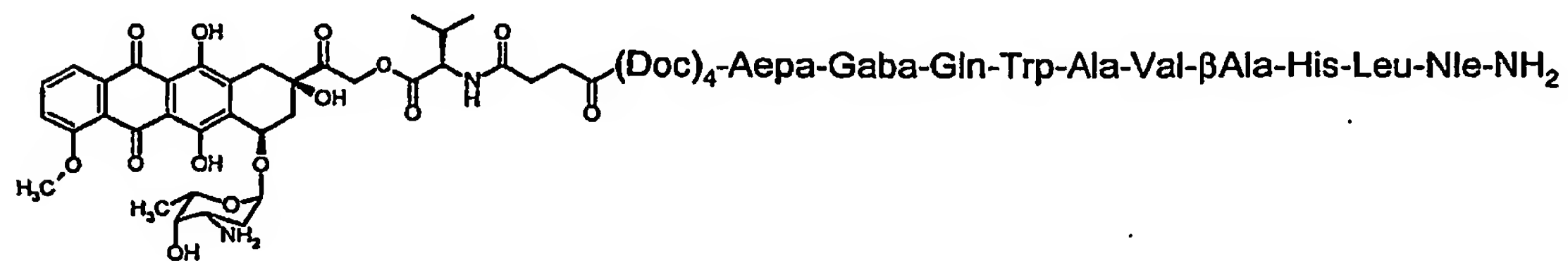
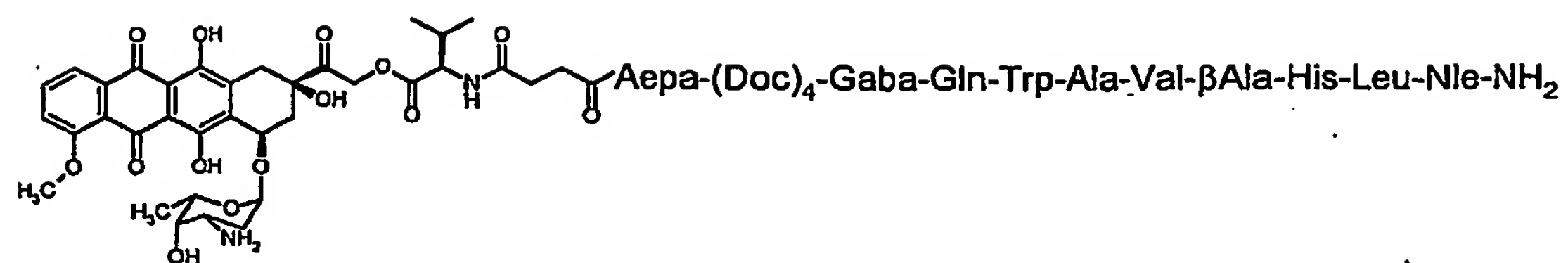
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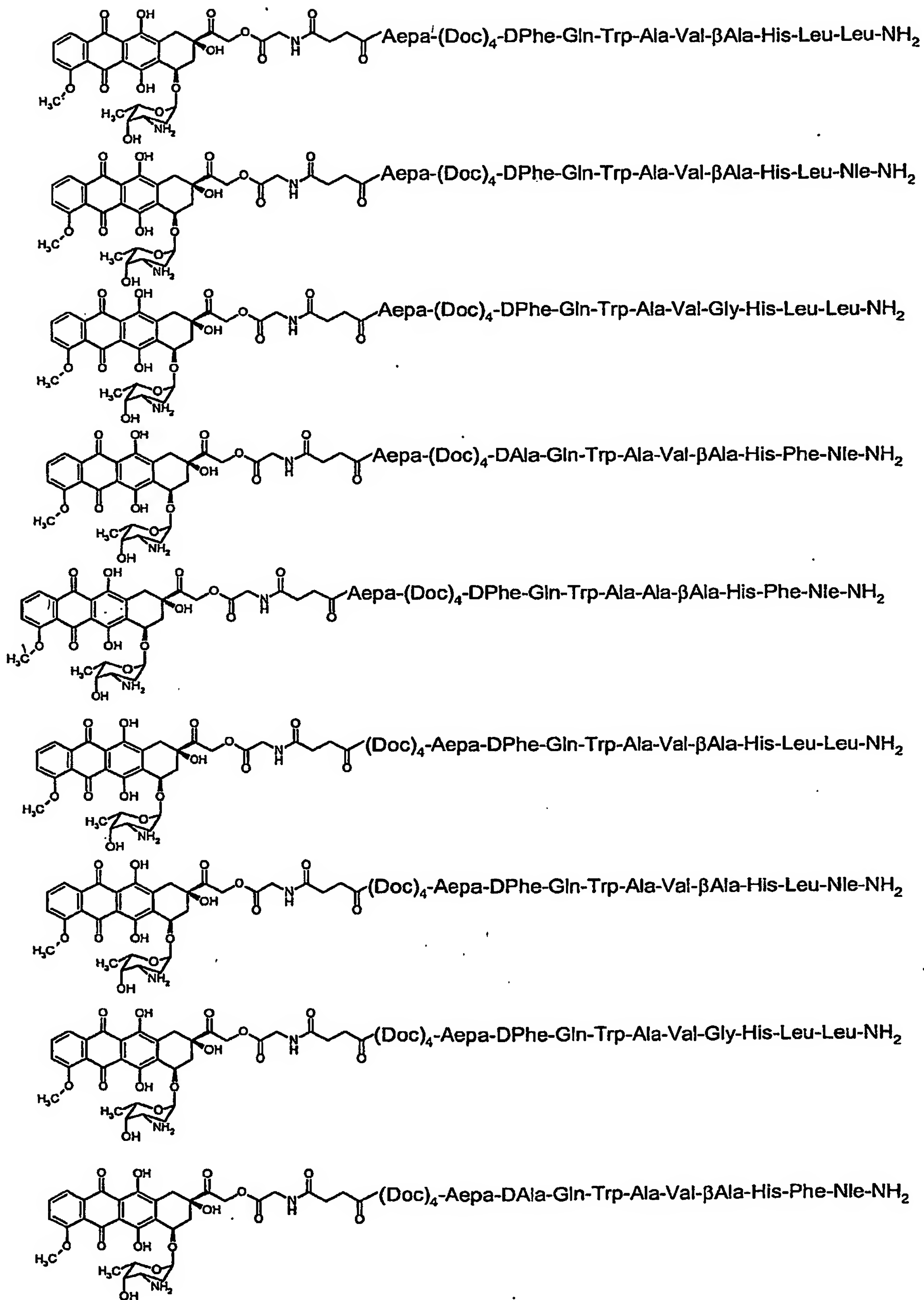
Appendix F

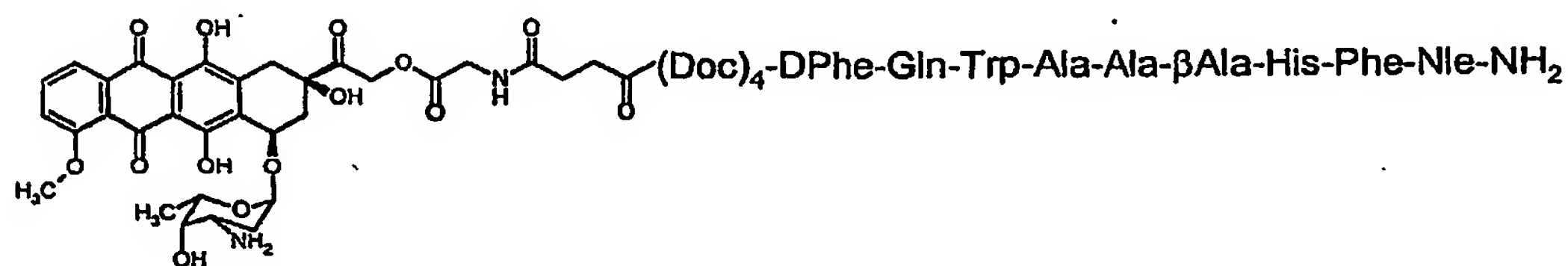
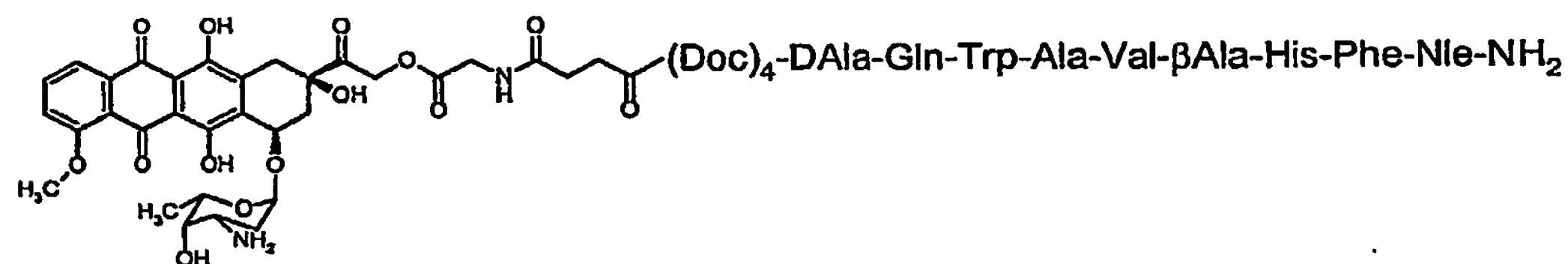
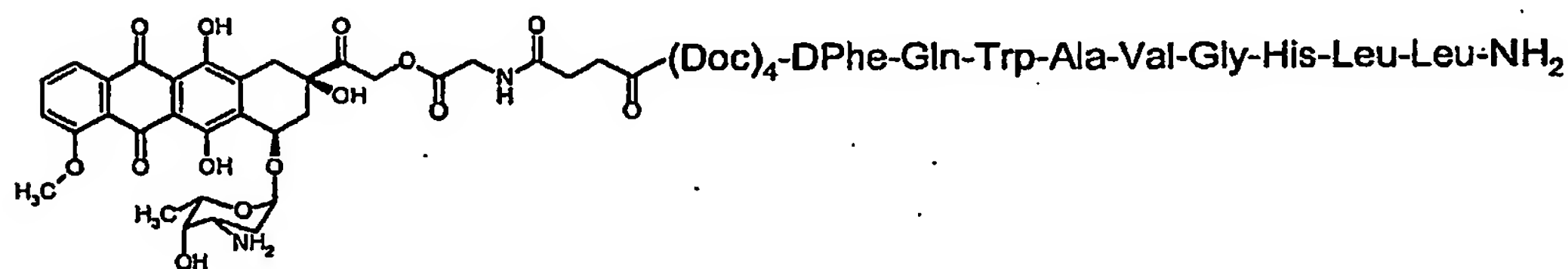
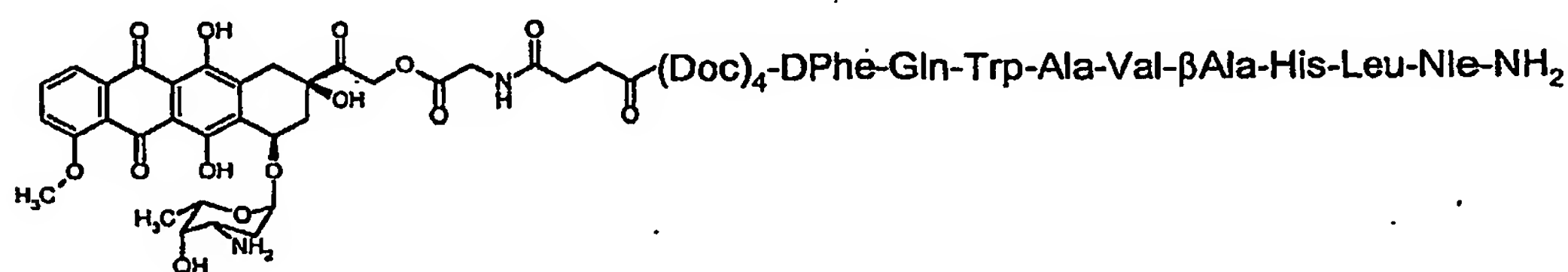
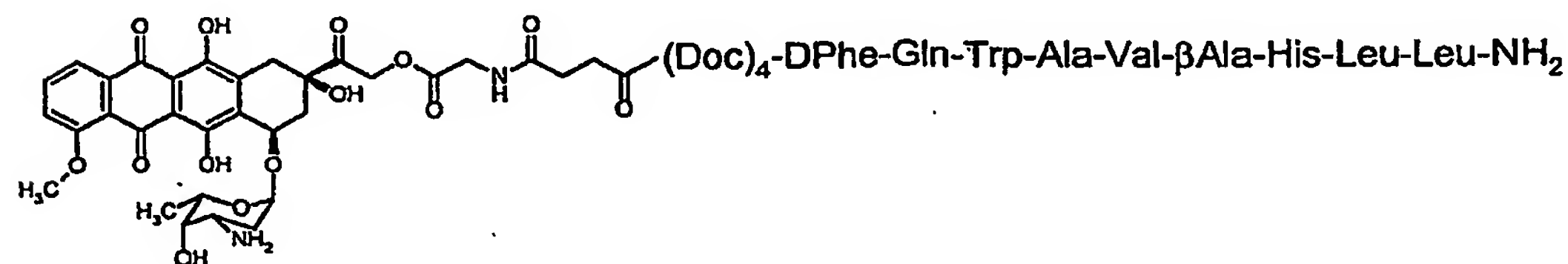
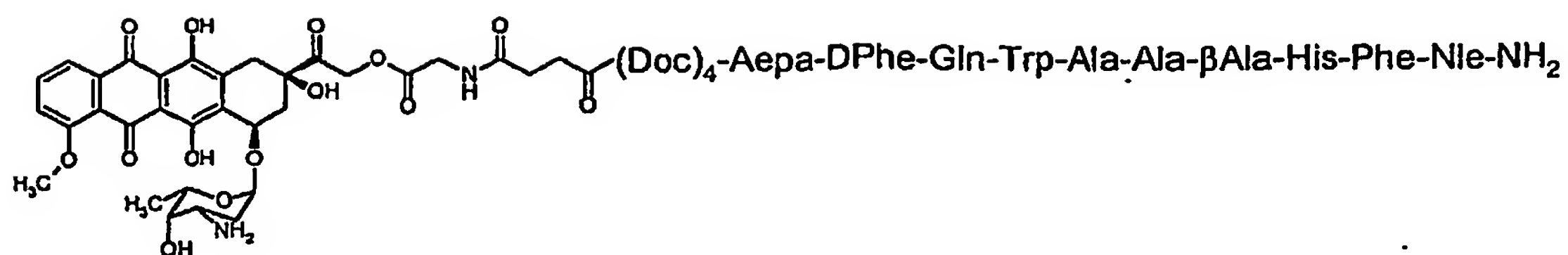


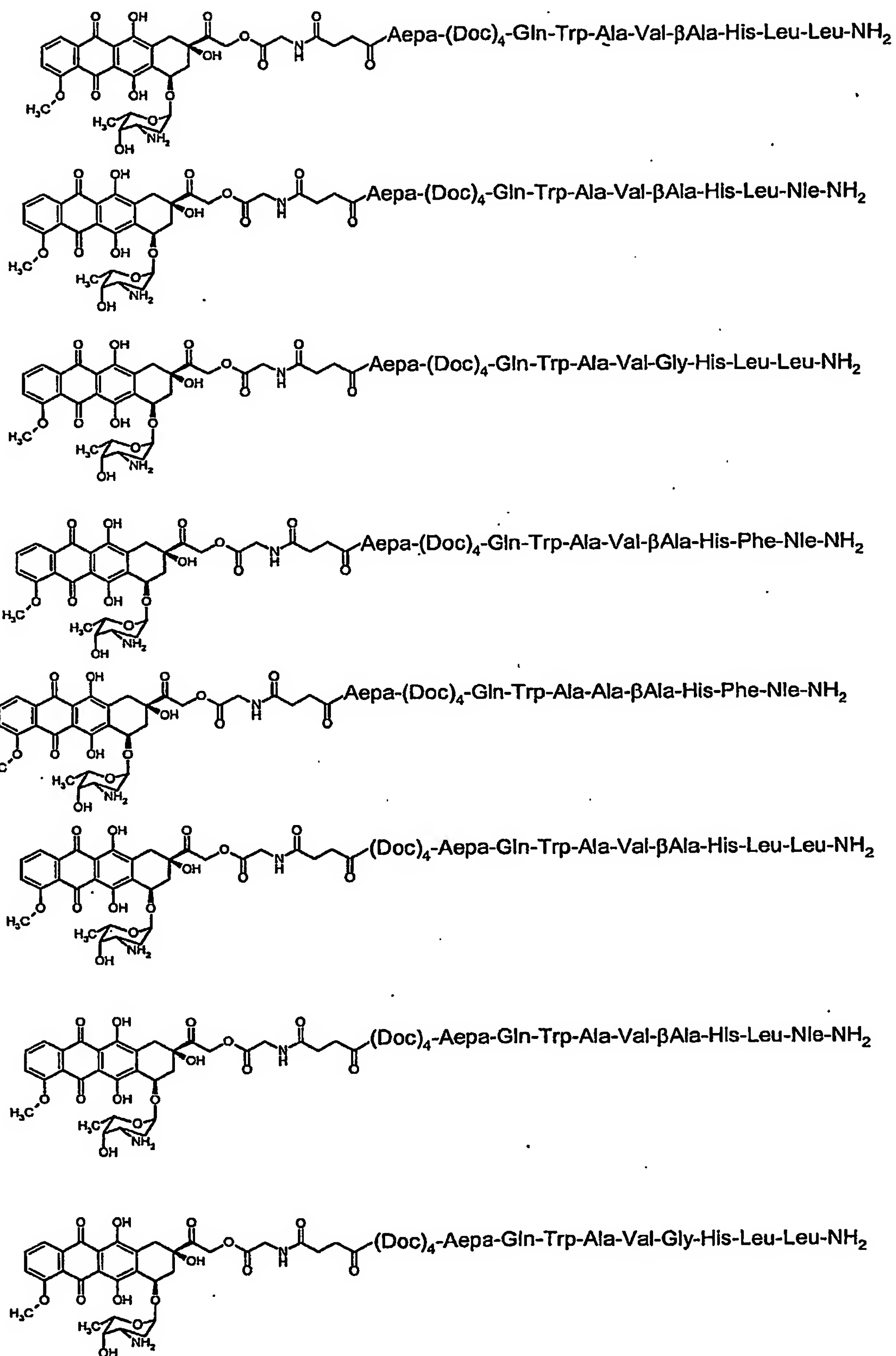
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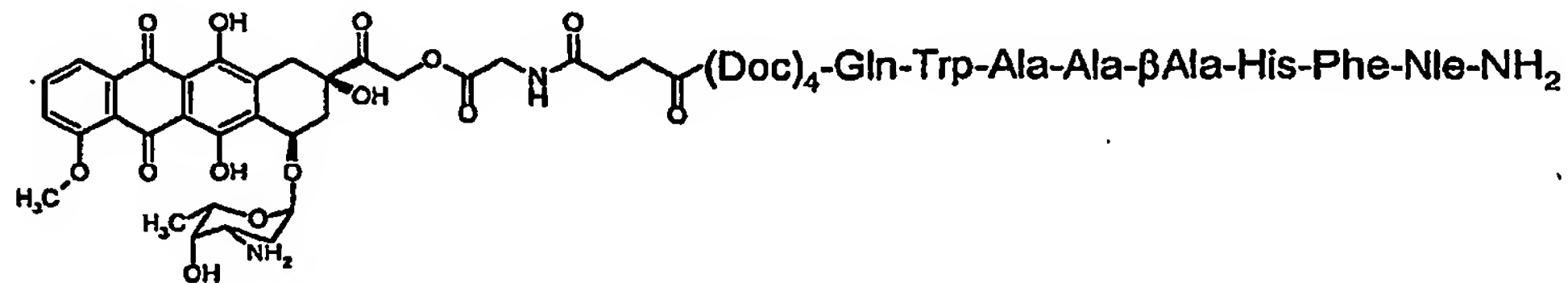
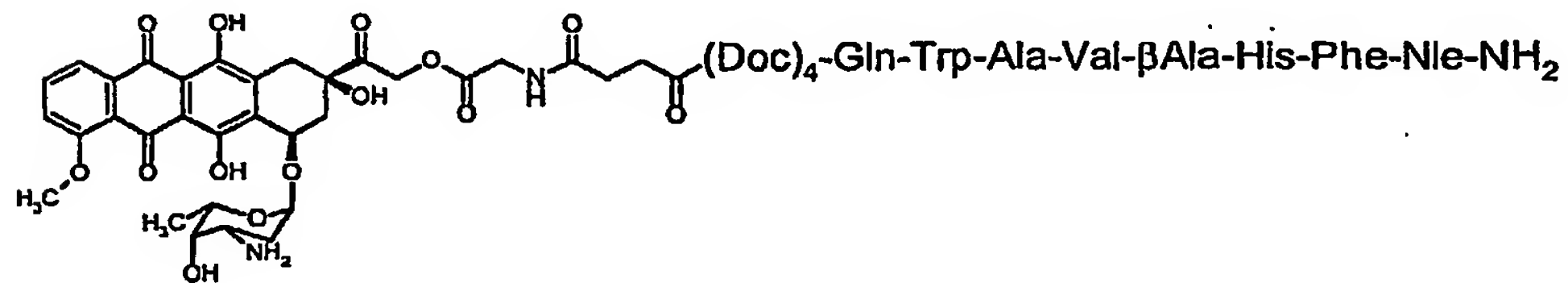
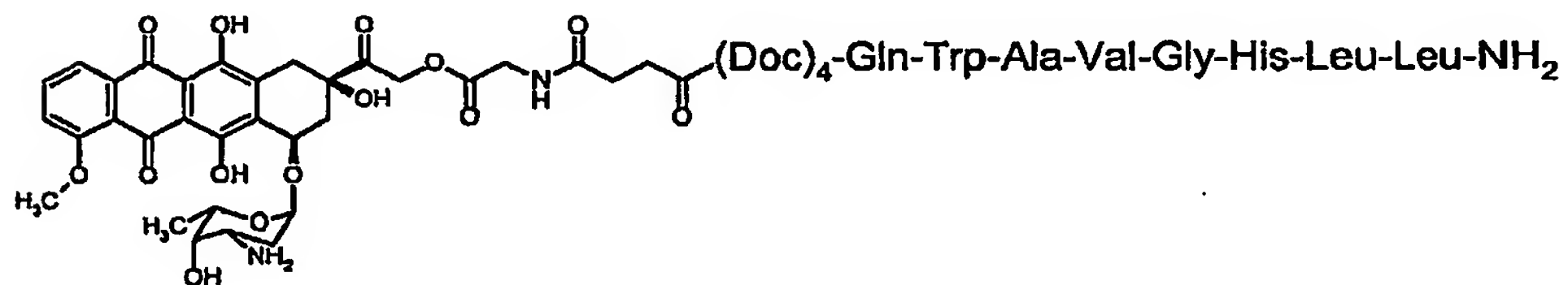
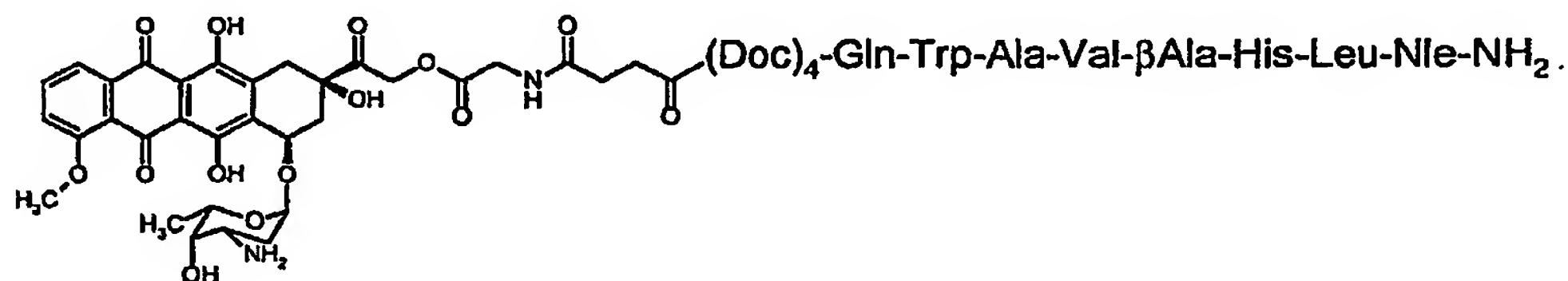
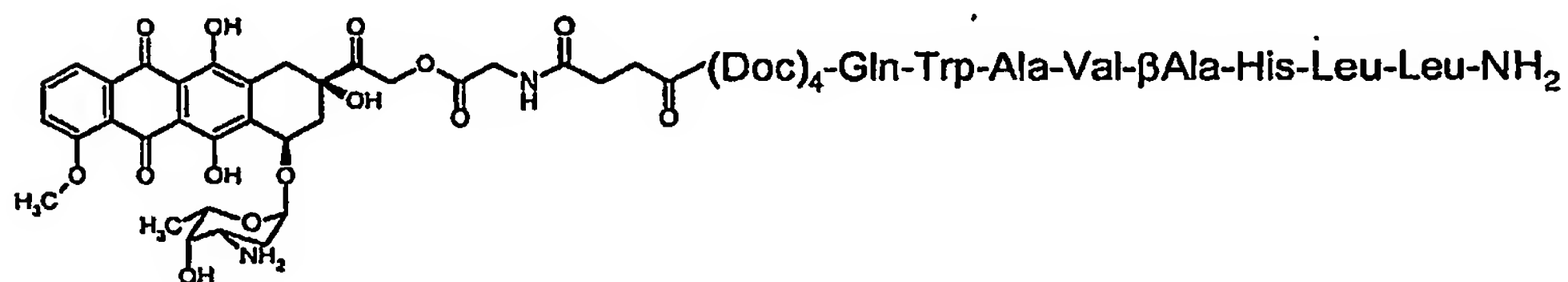
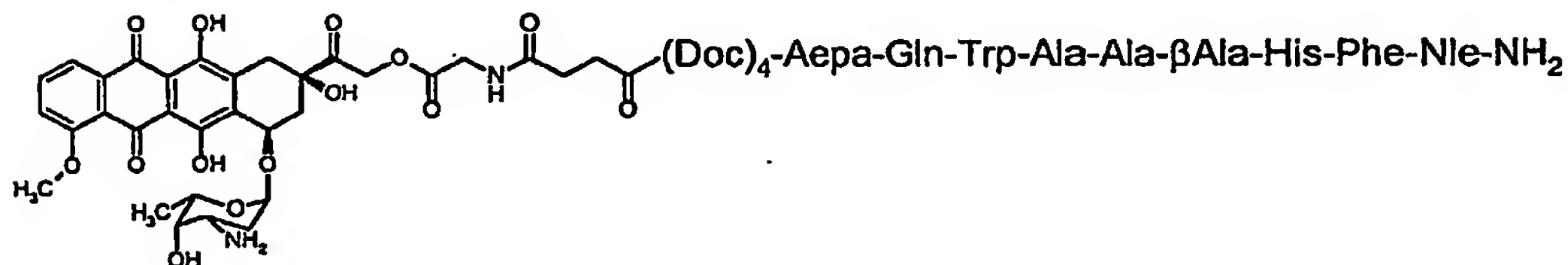
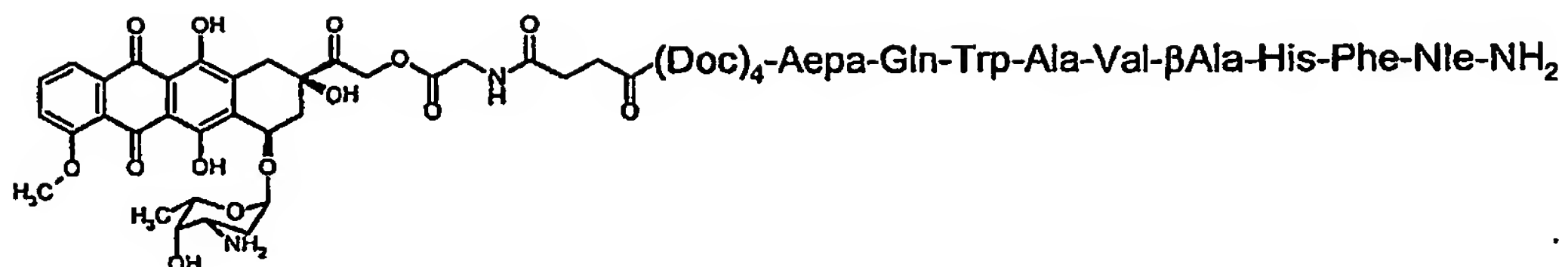


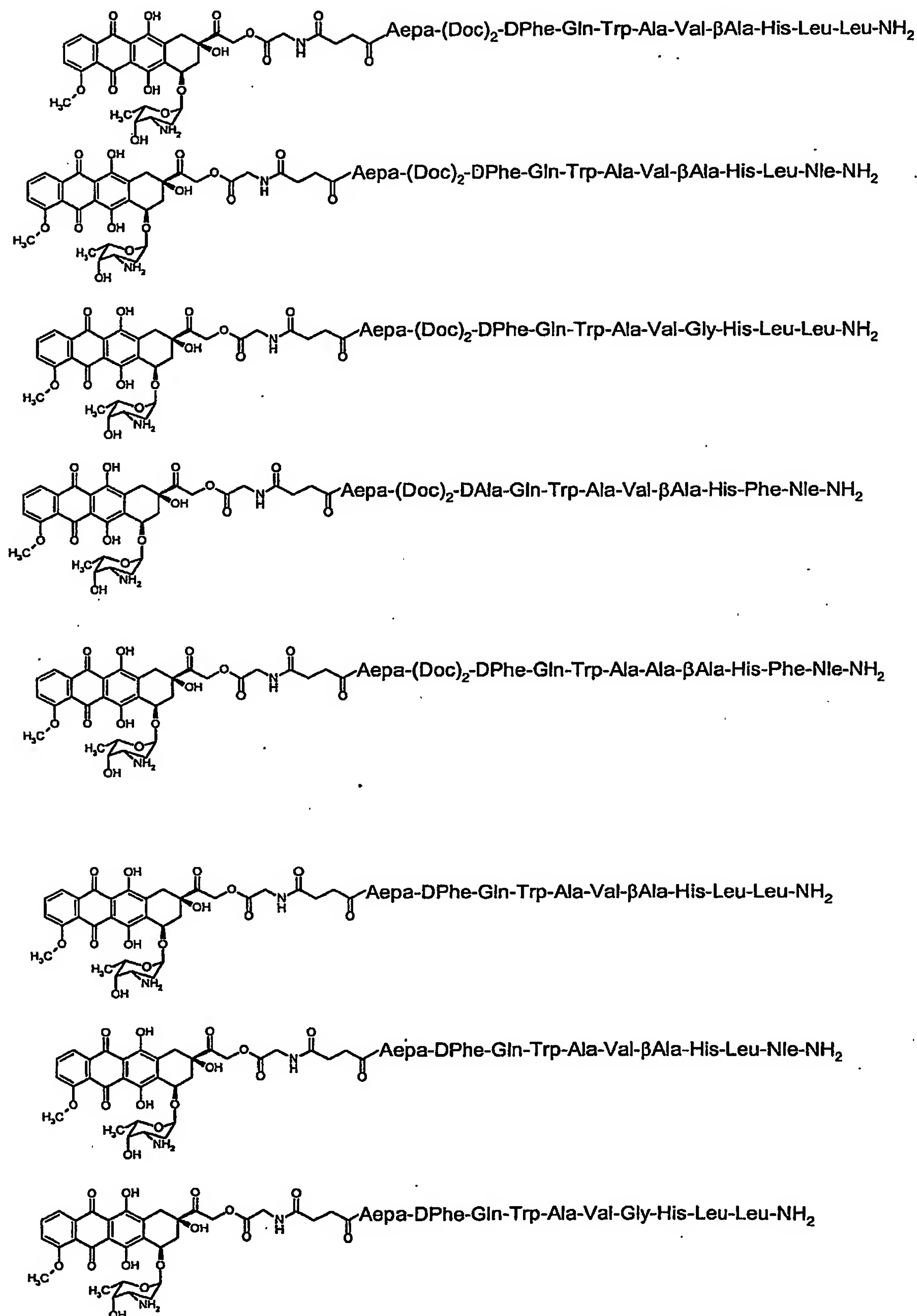
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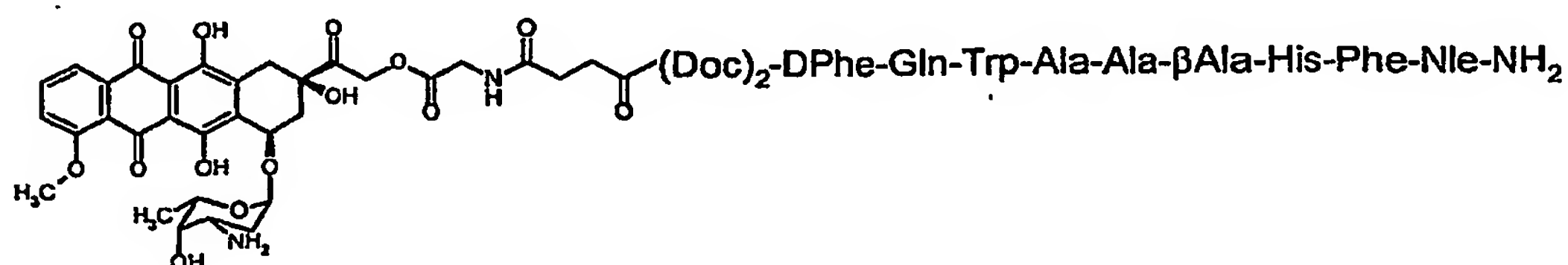
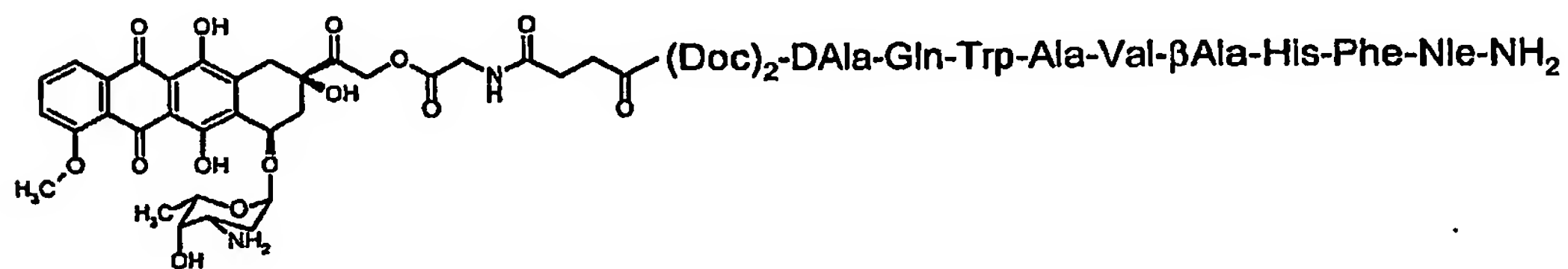
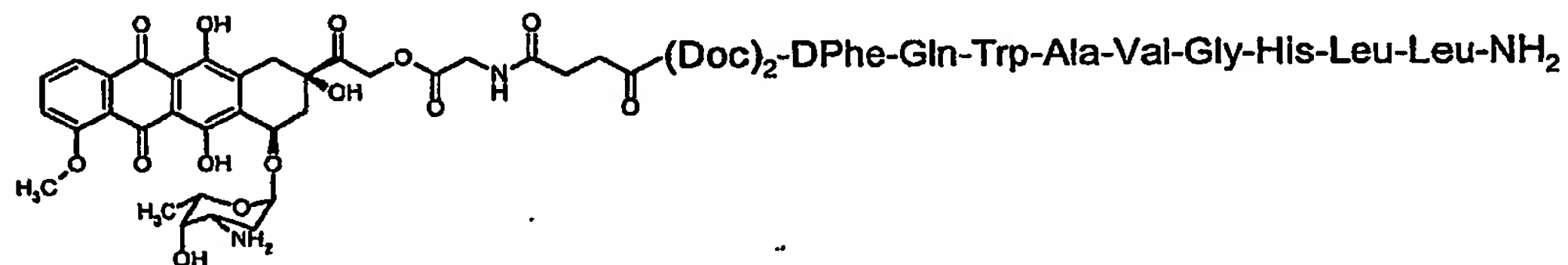
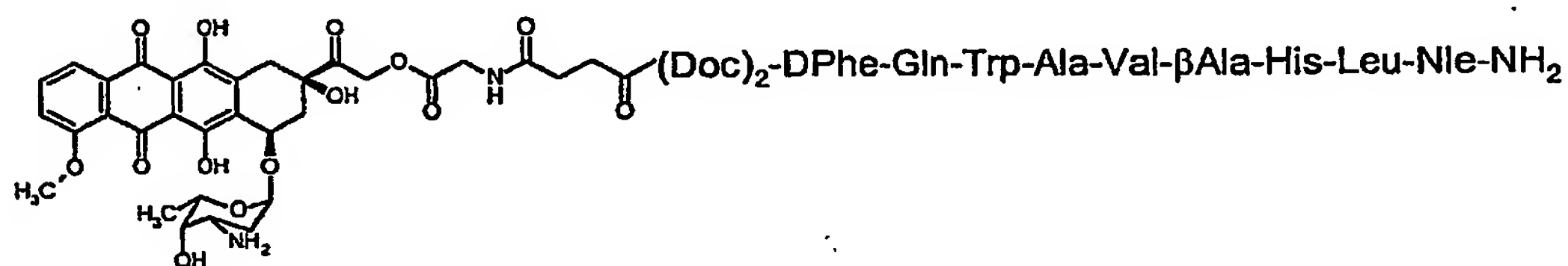
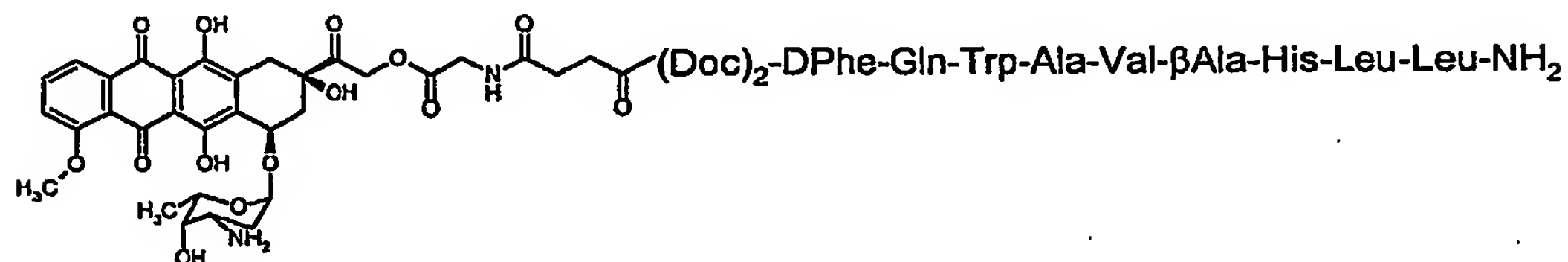
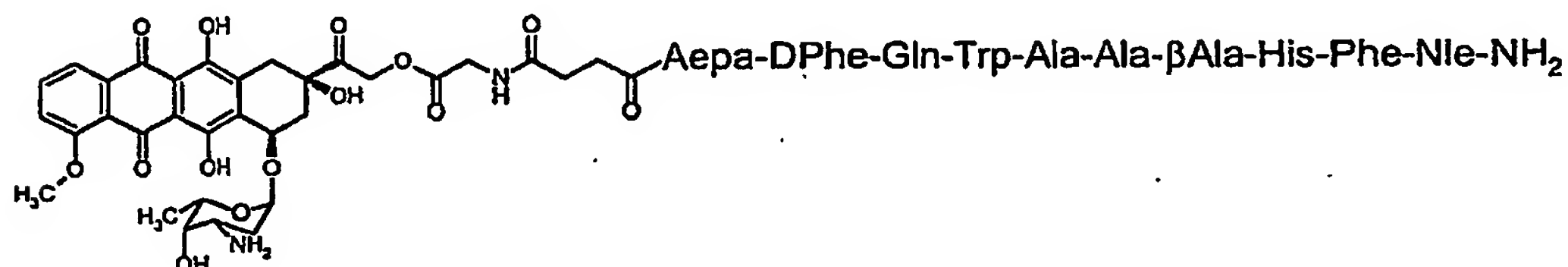
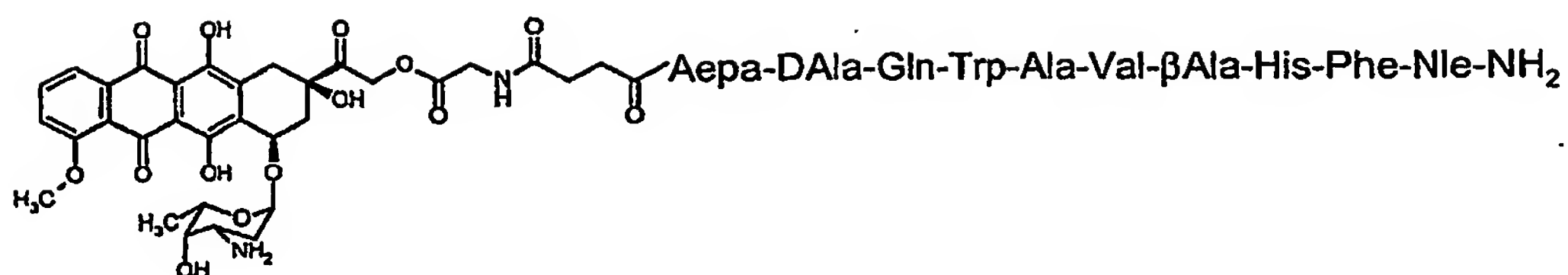


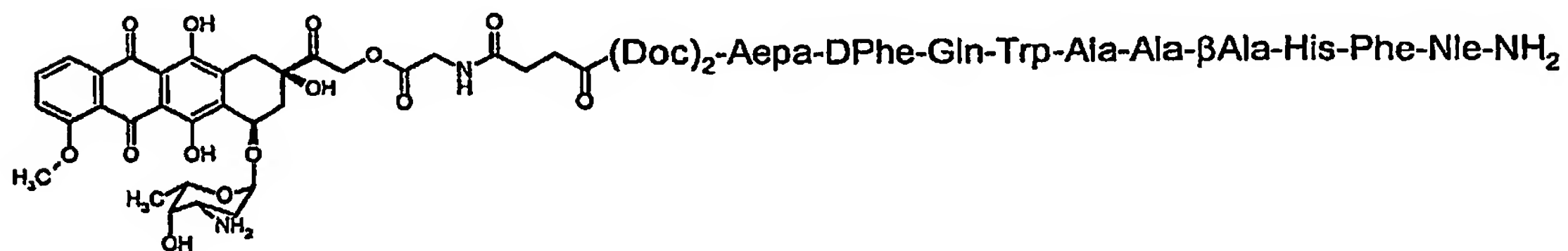
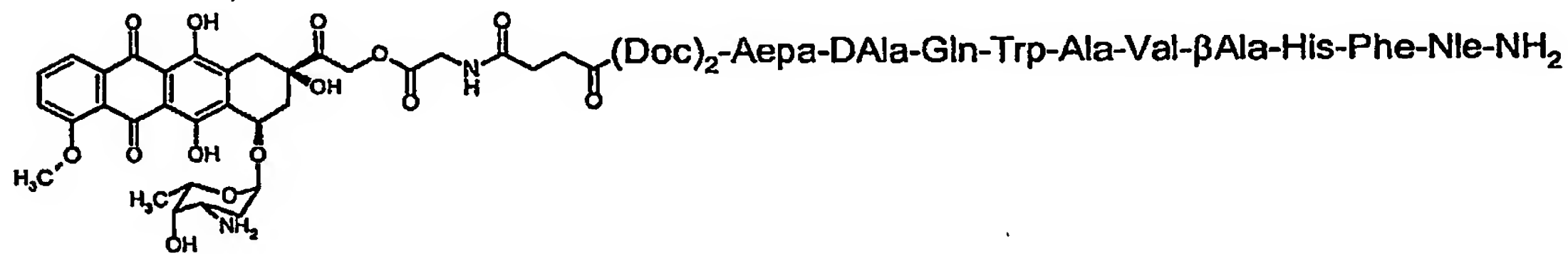
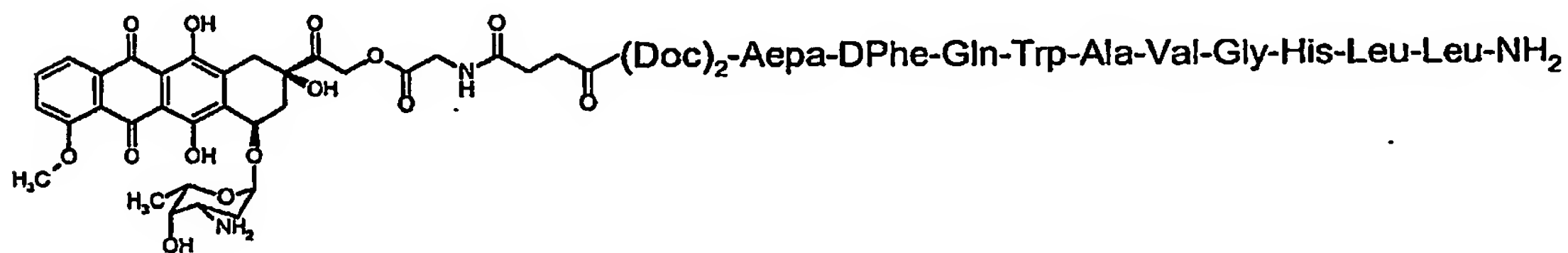
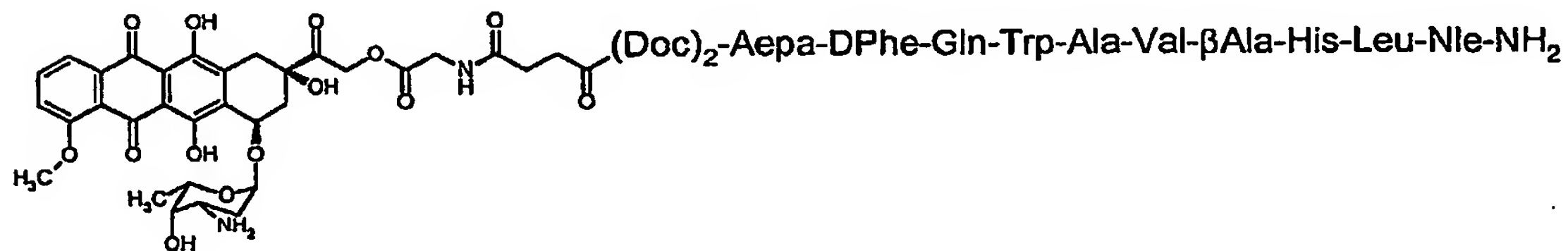
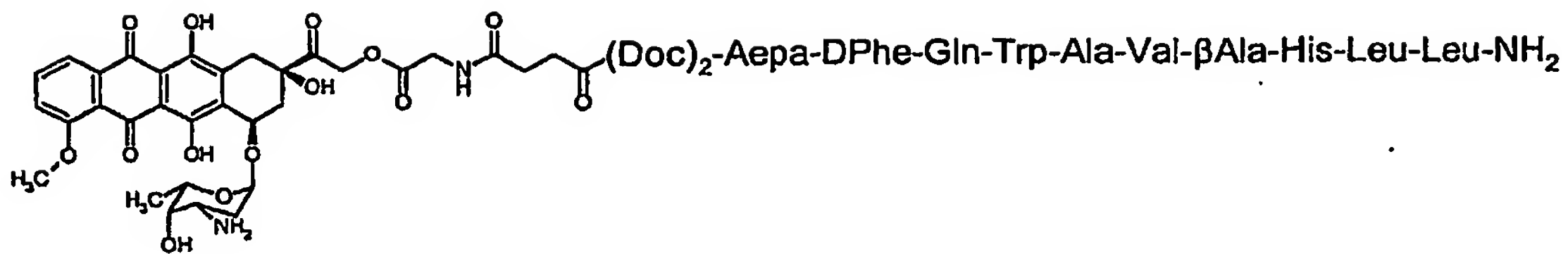


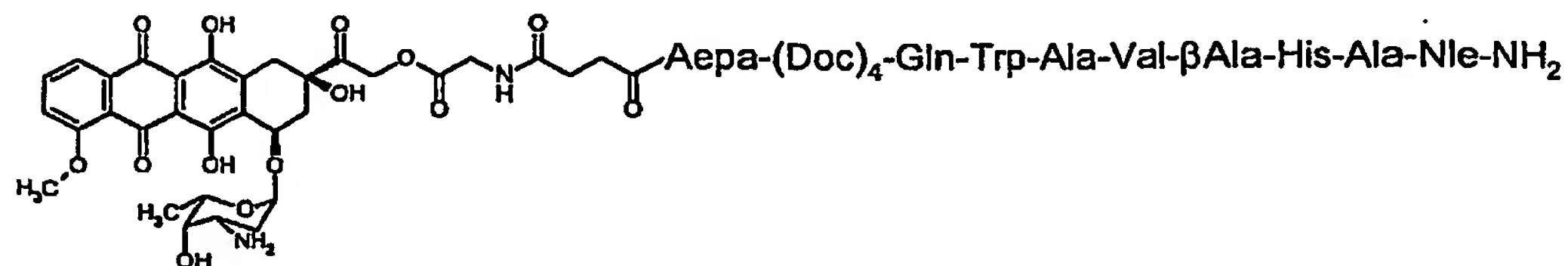
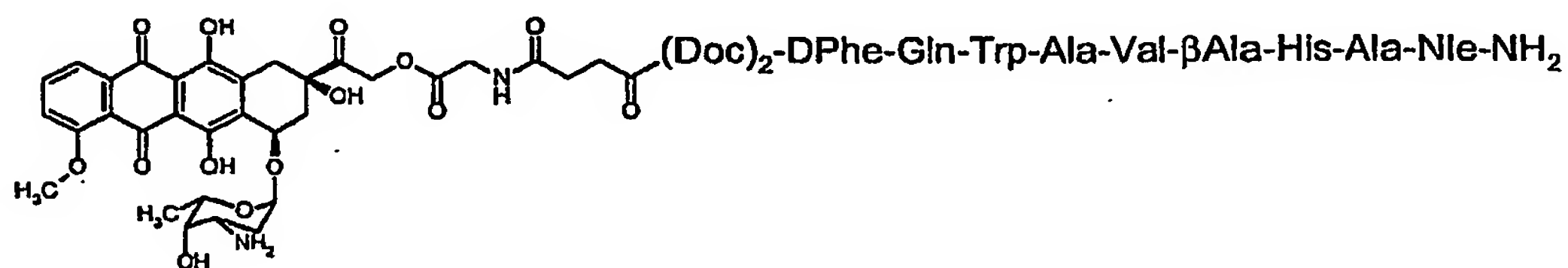
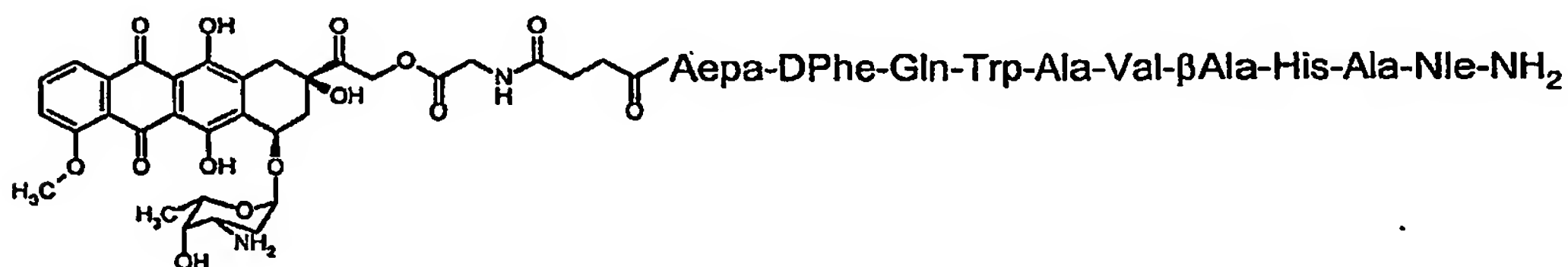
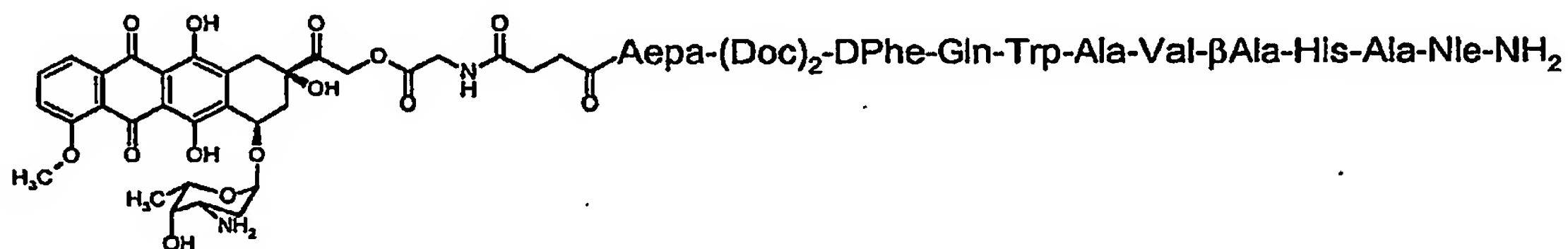
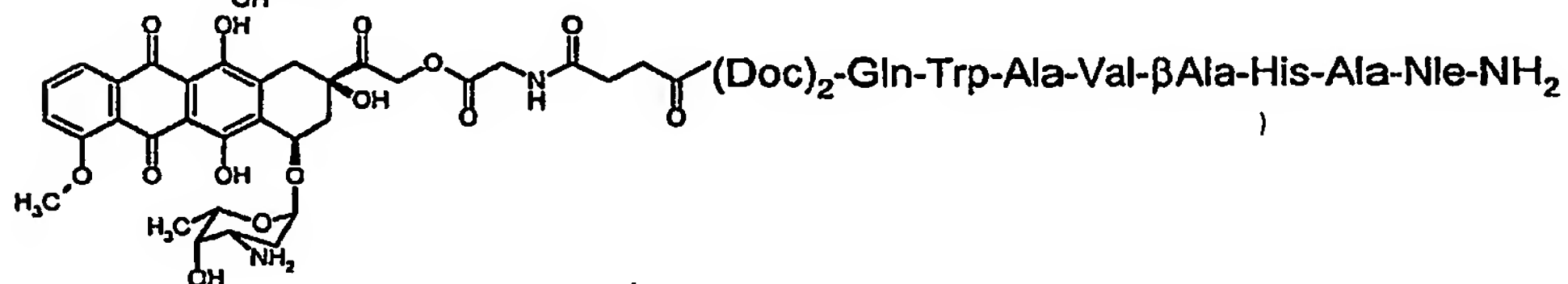
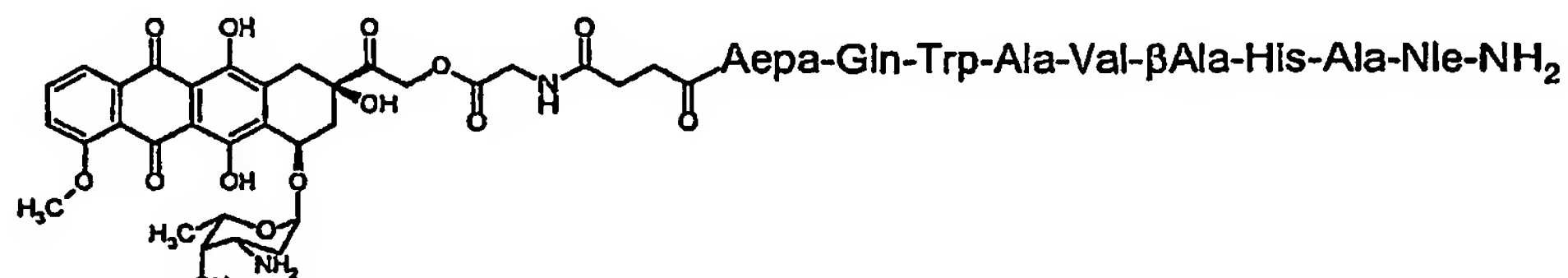
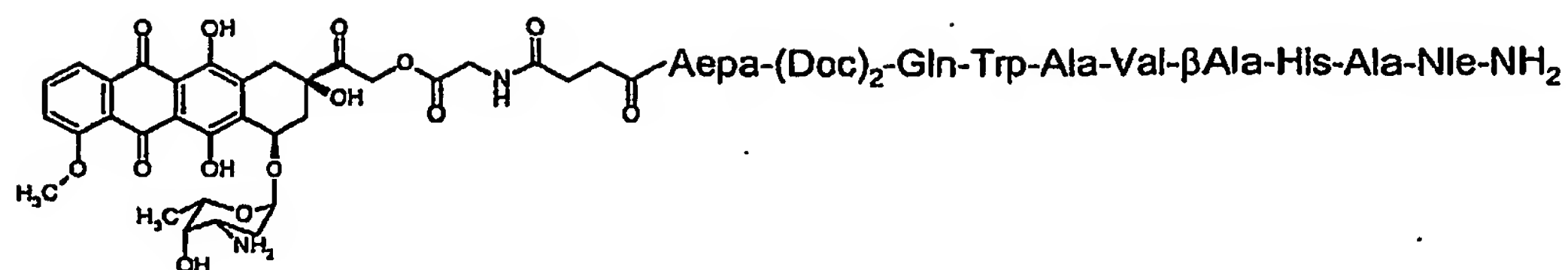


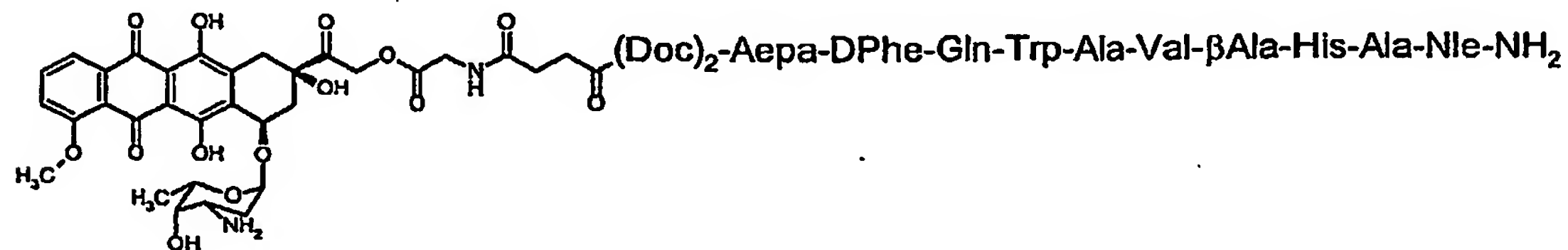
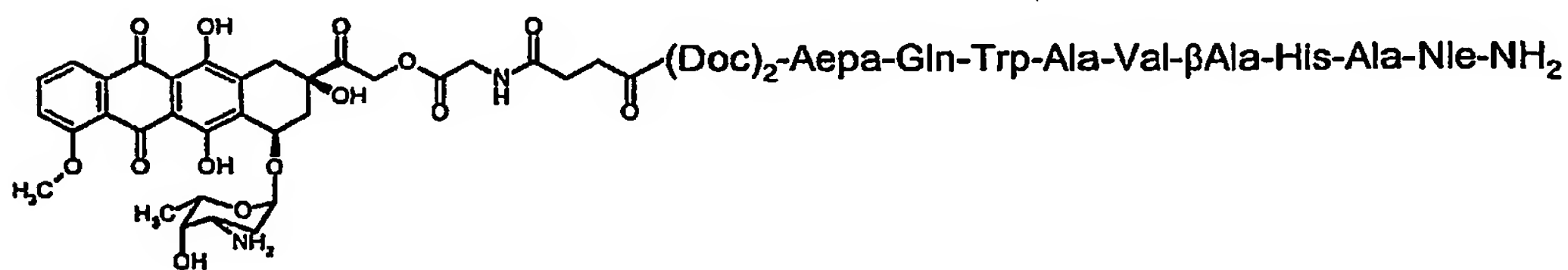
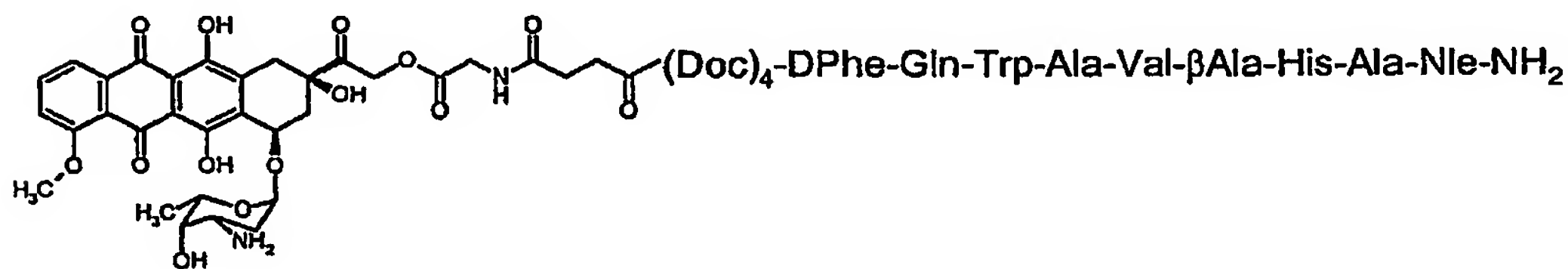
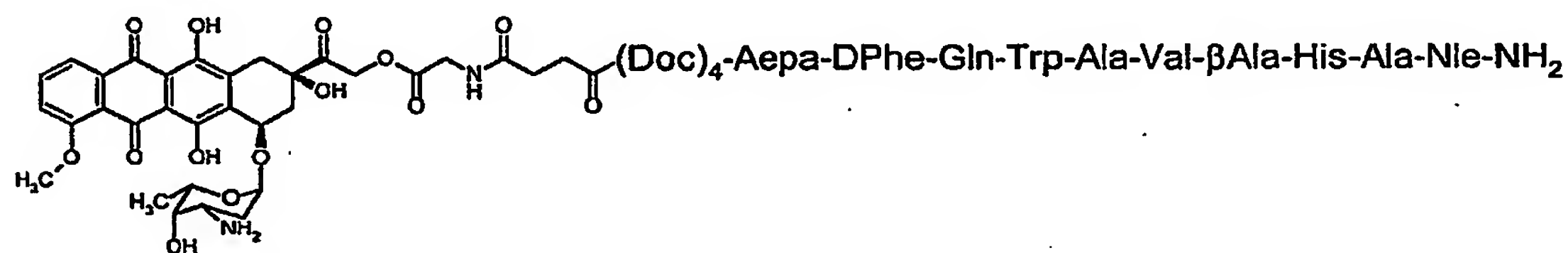
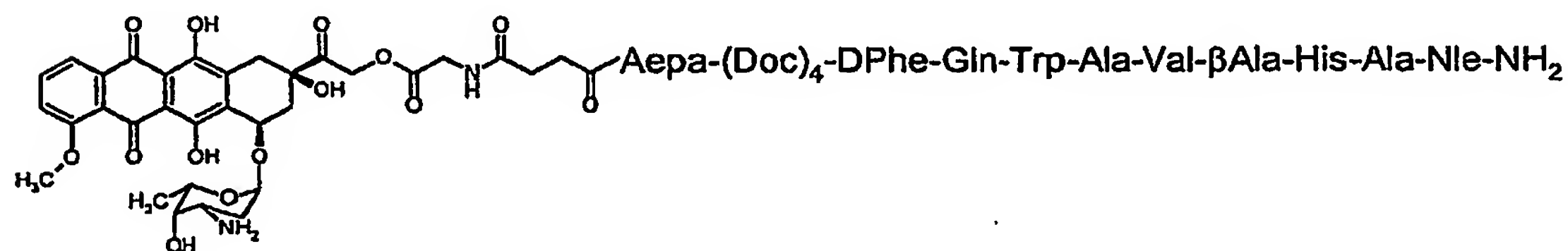
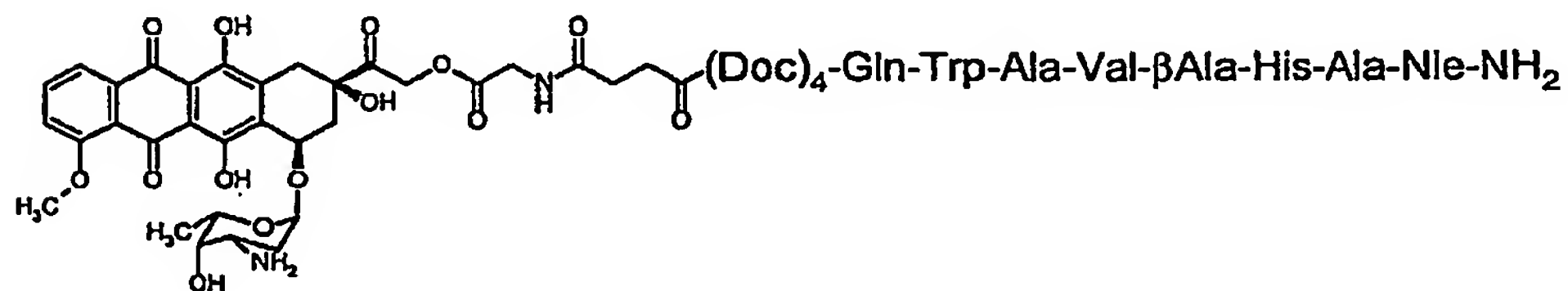
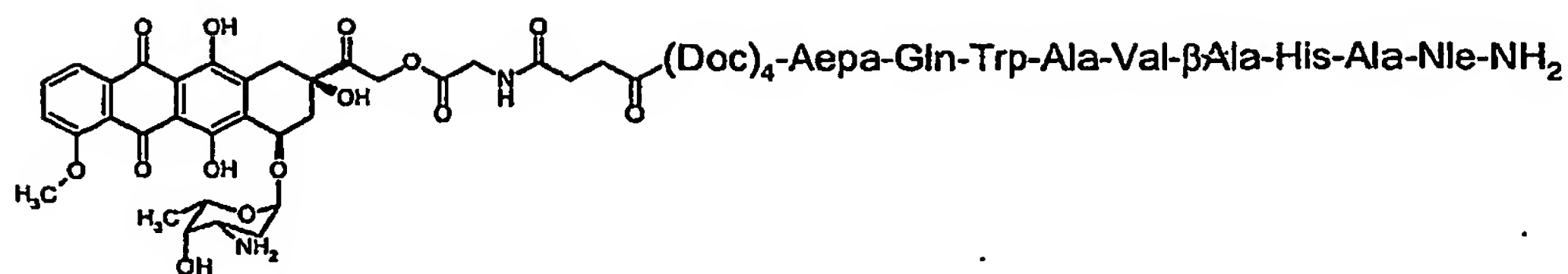


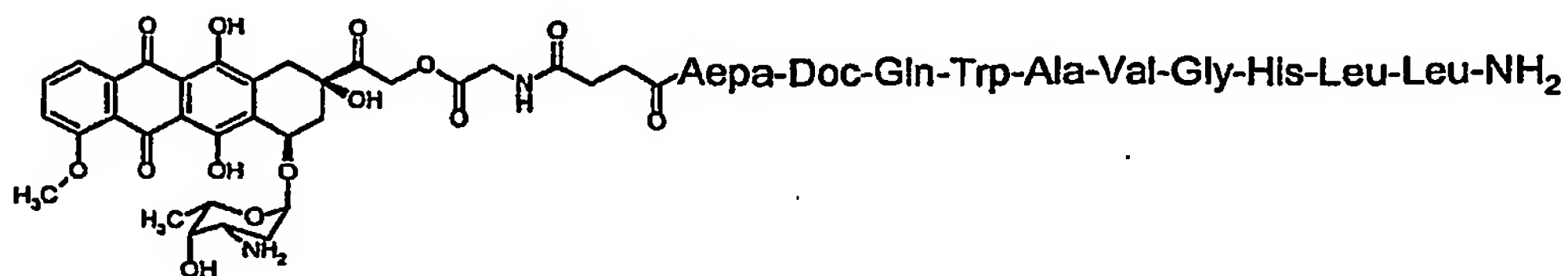
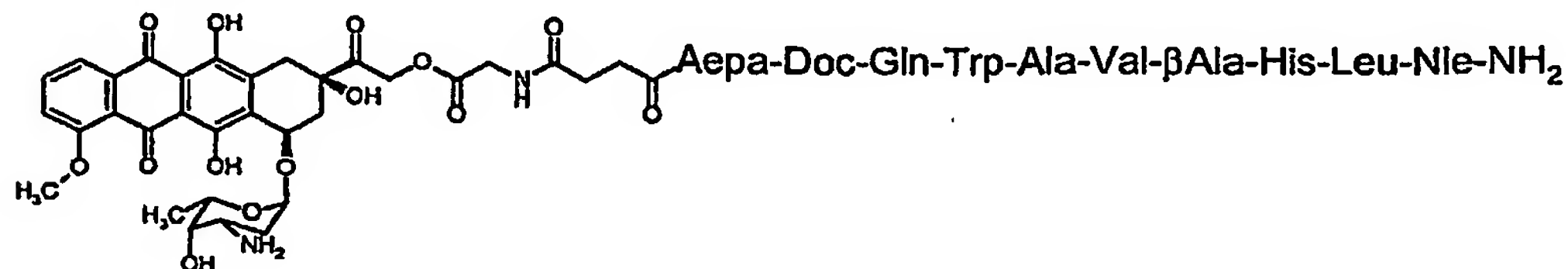
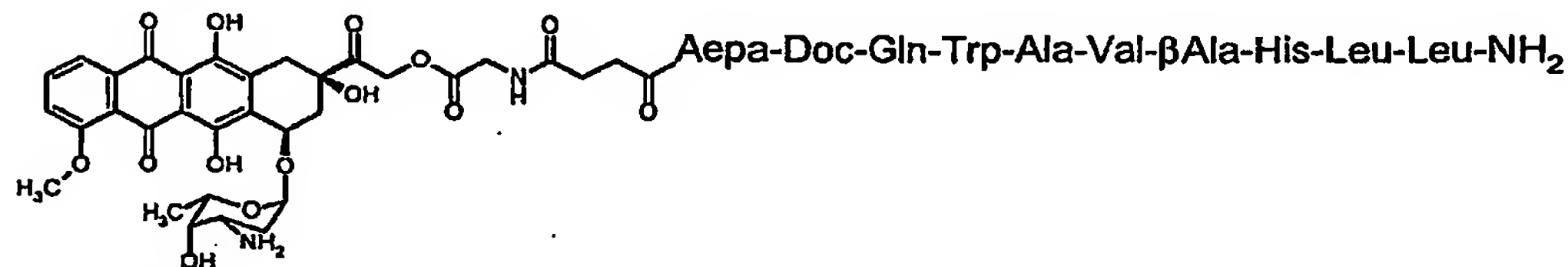
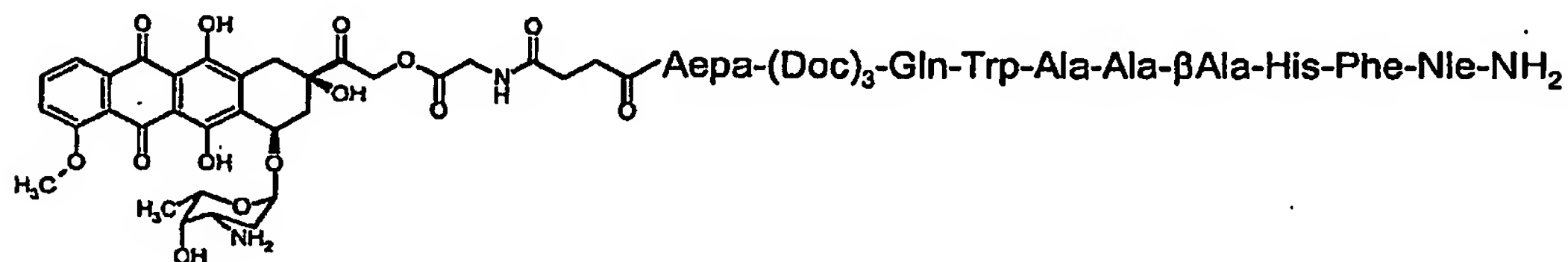
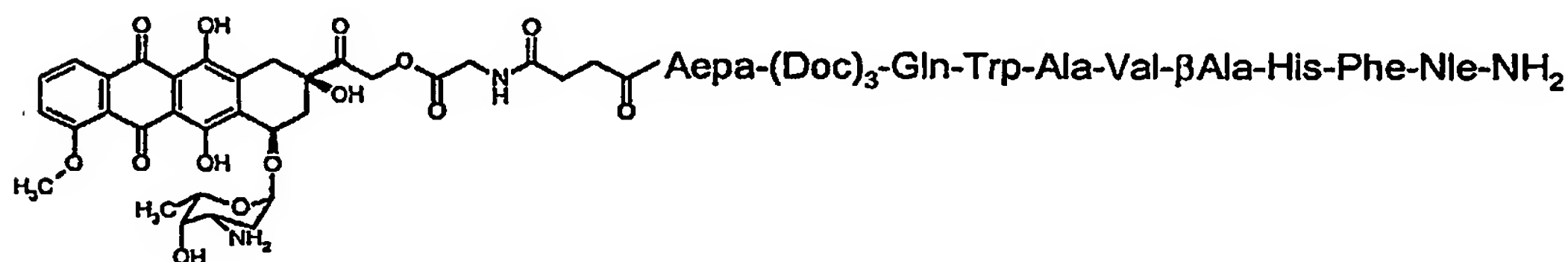
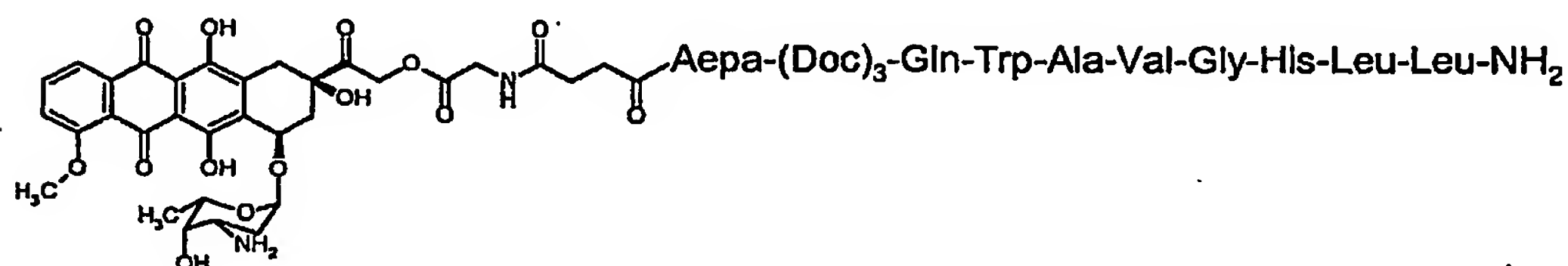
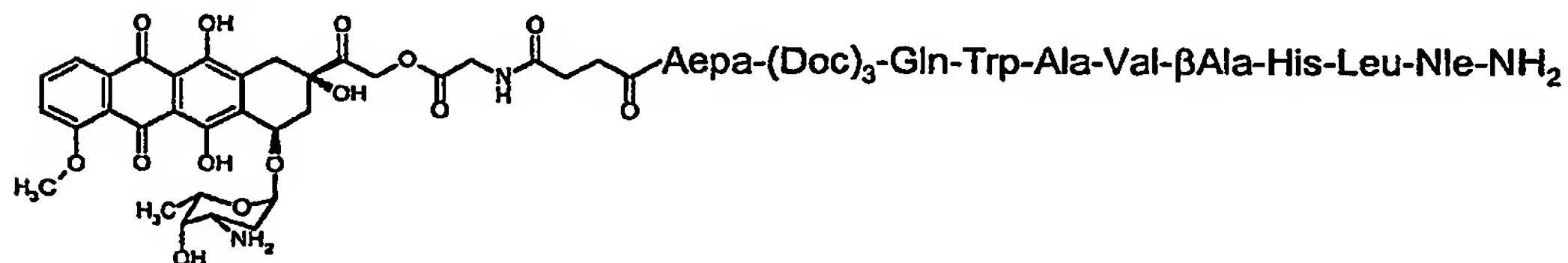
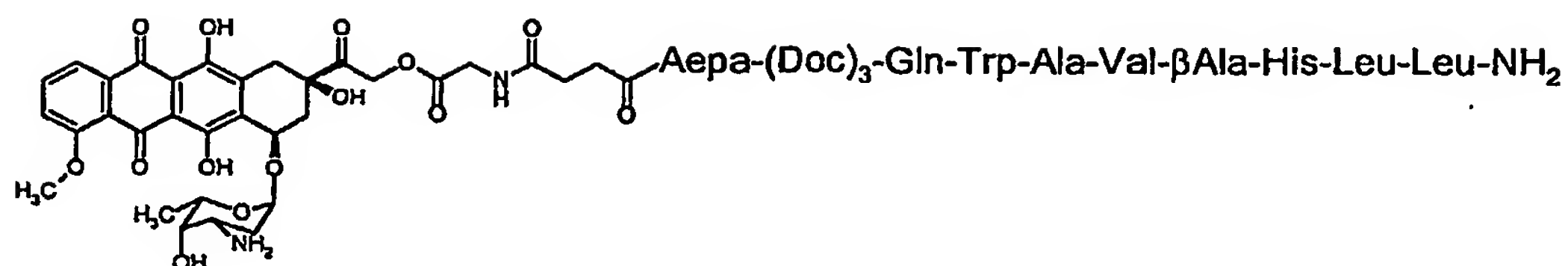


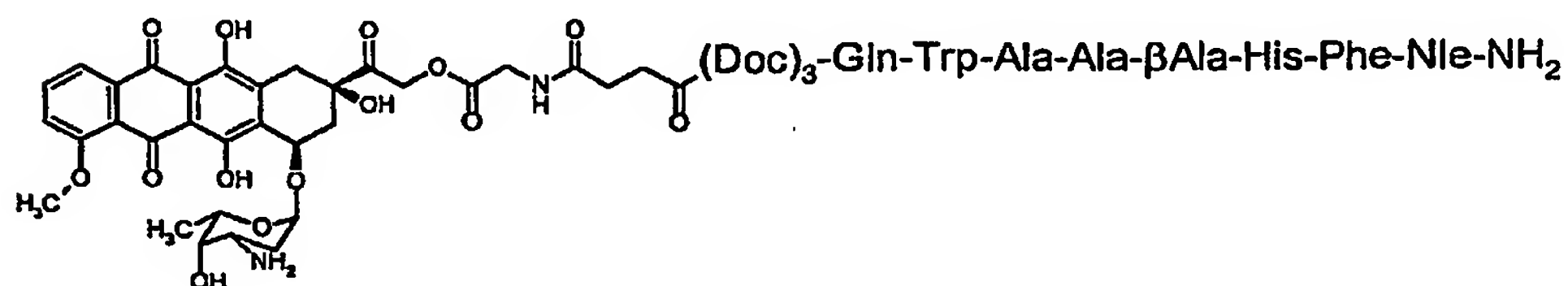
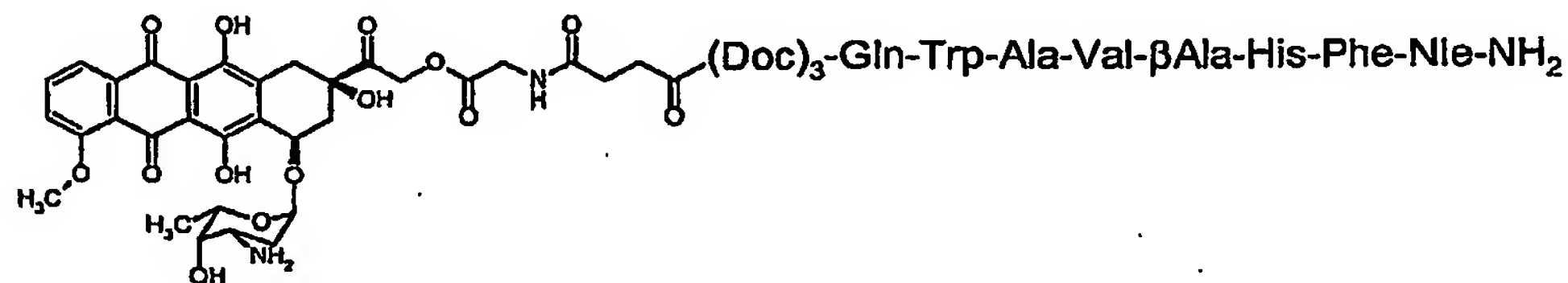
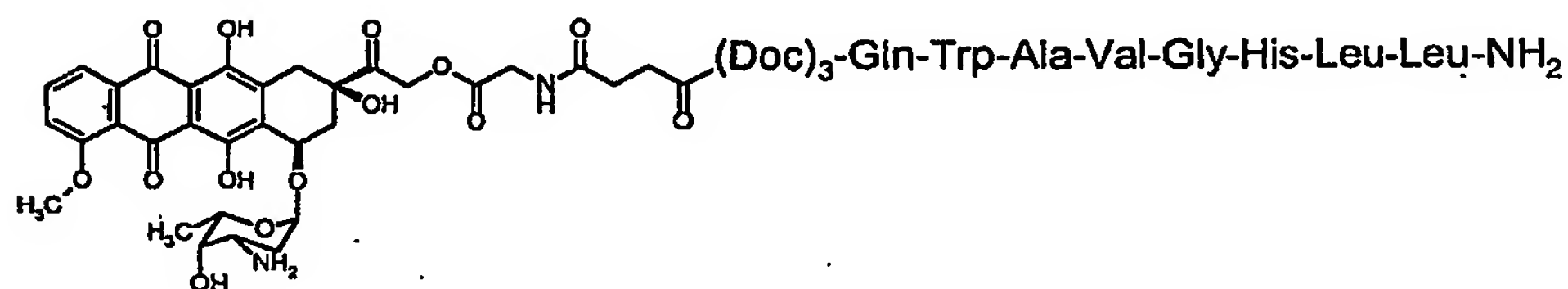
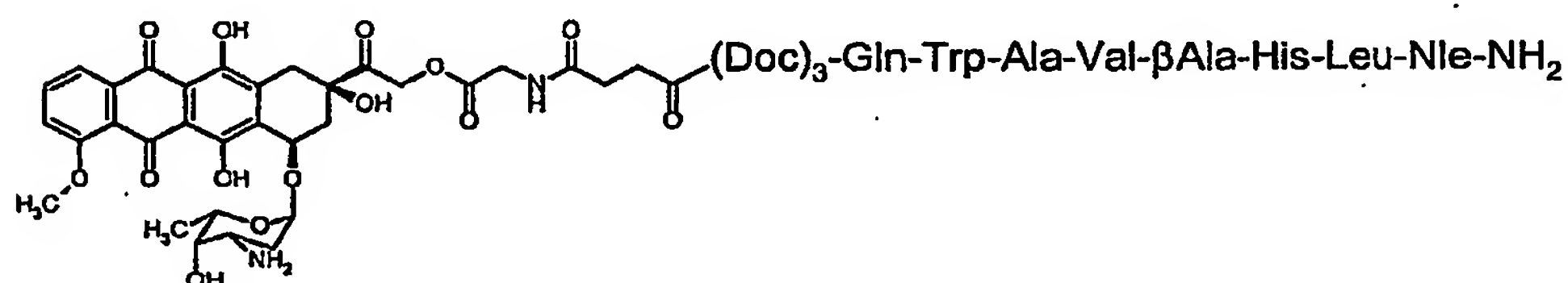
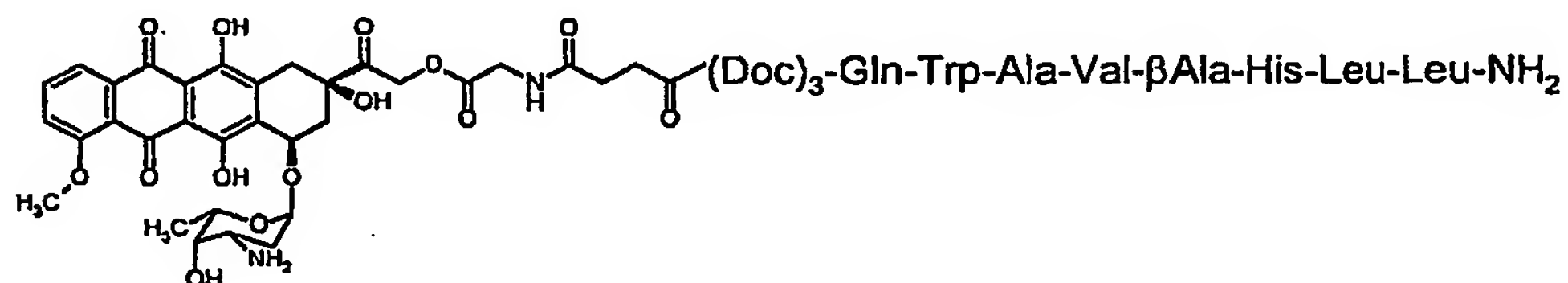
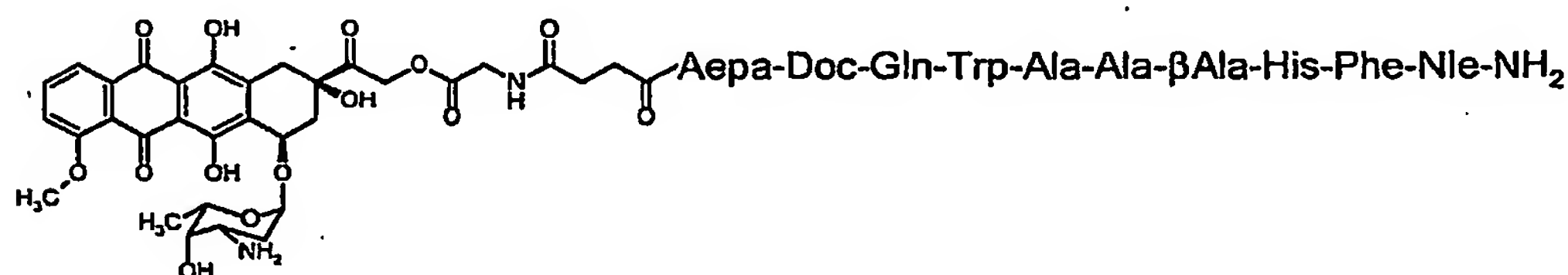
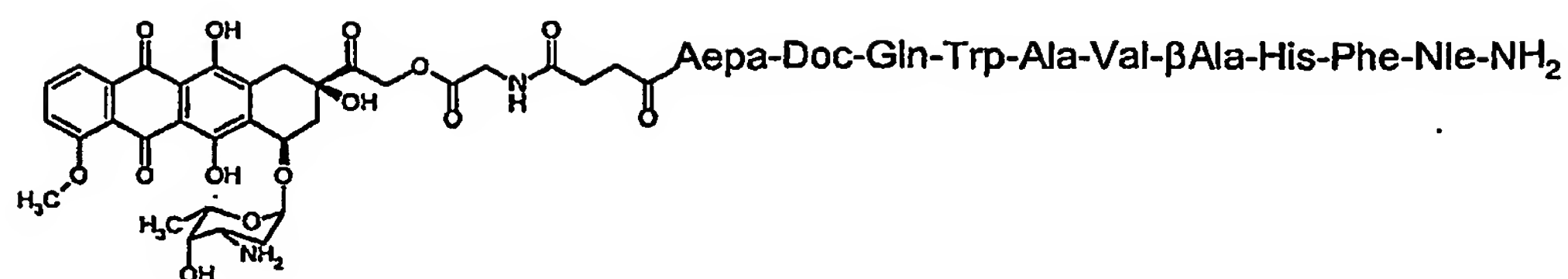


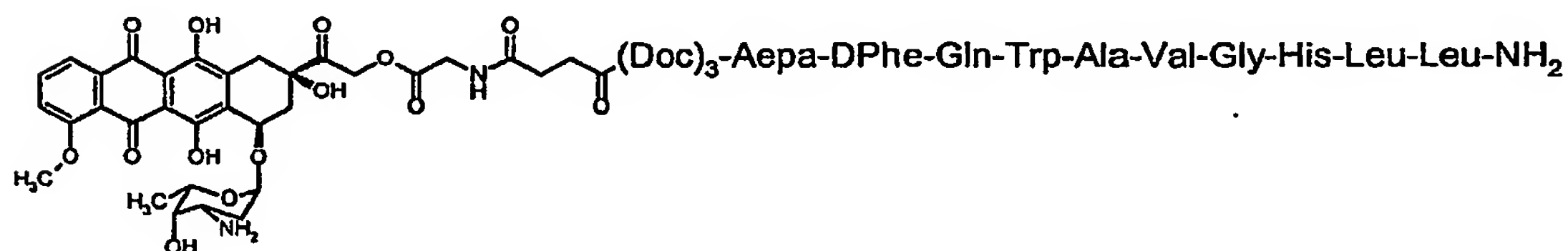
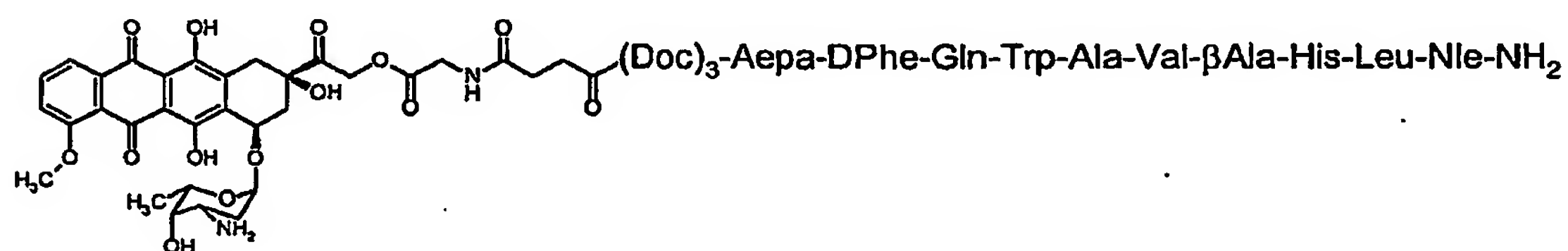
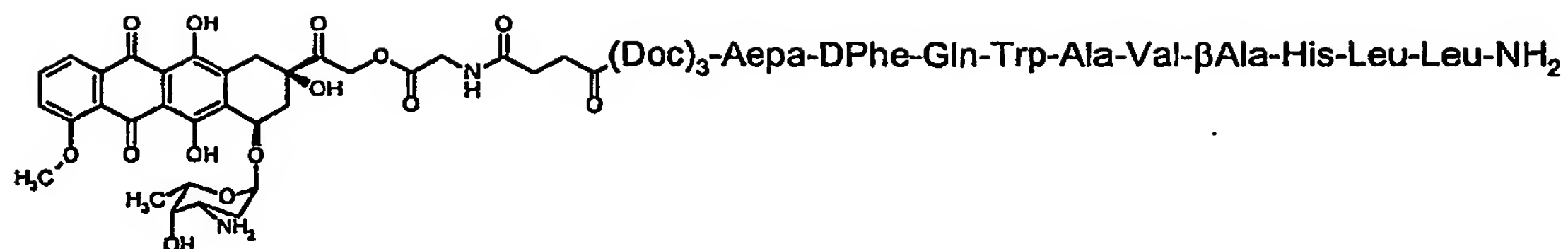


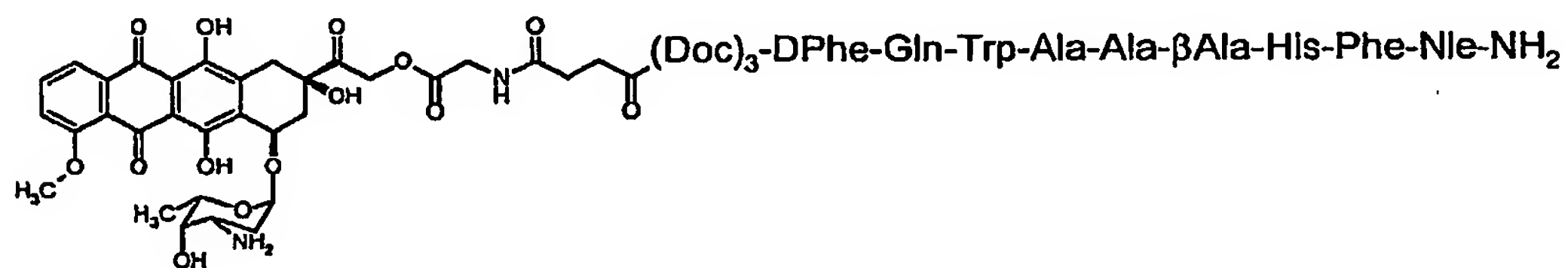
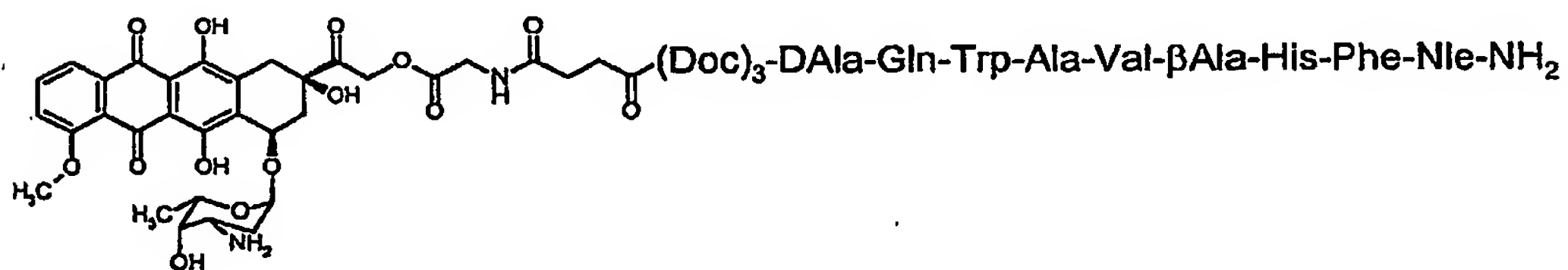
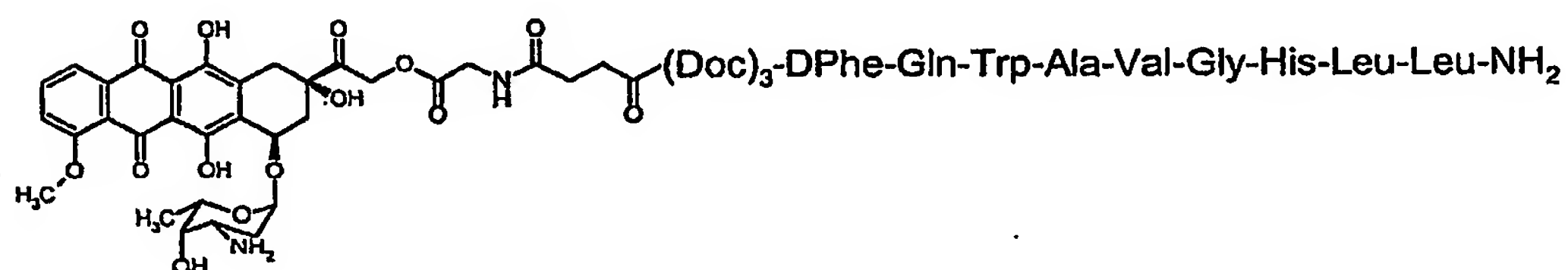
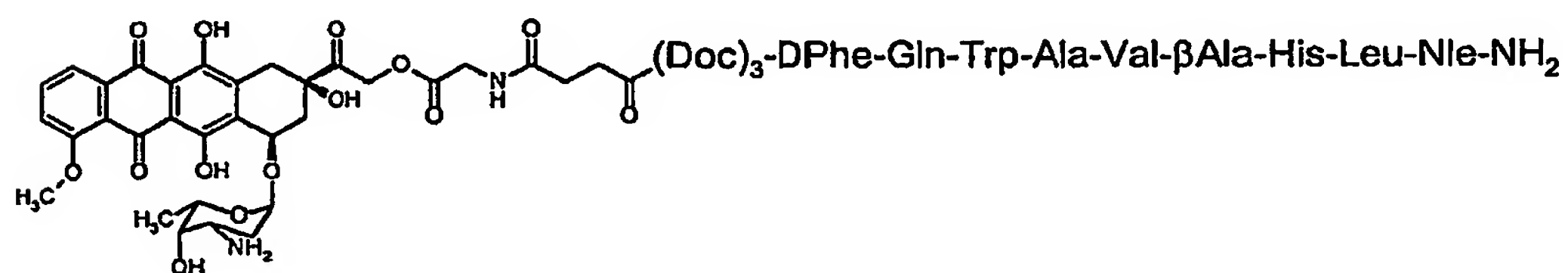
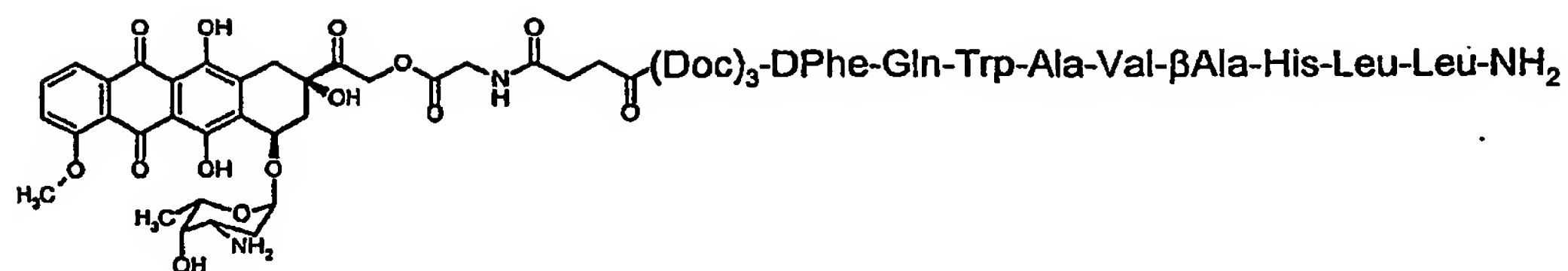


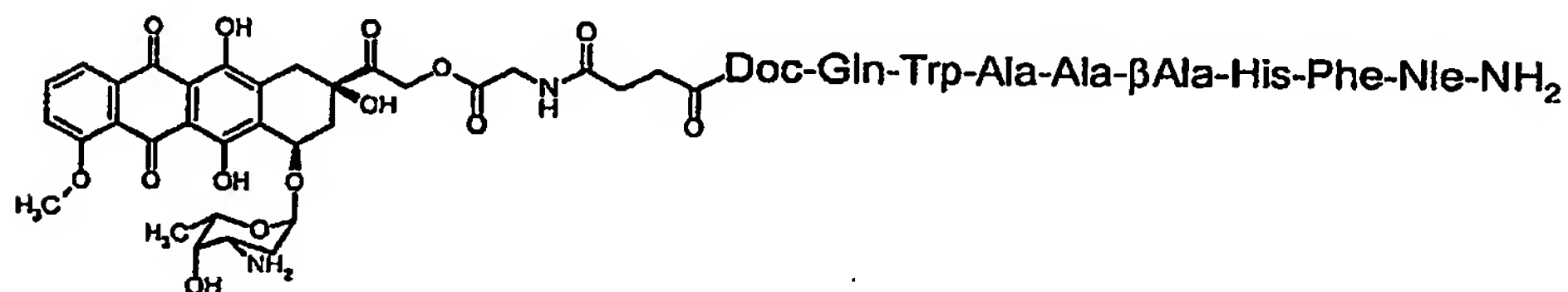
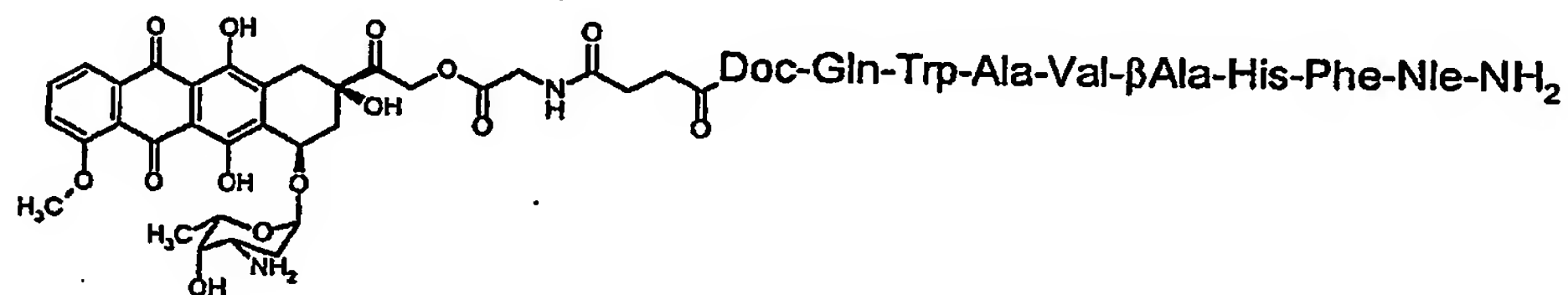
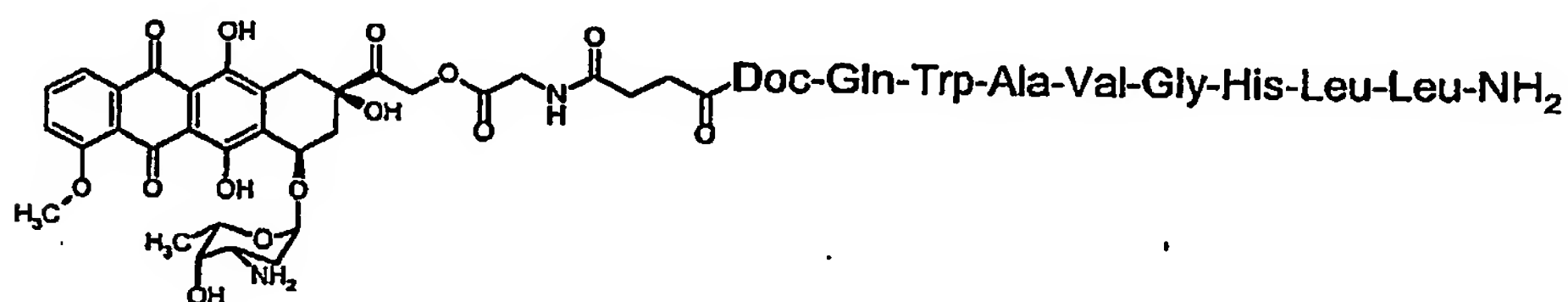
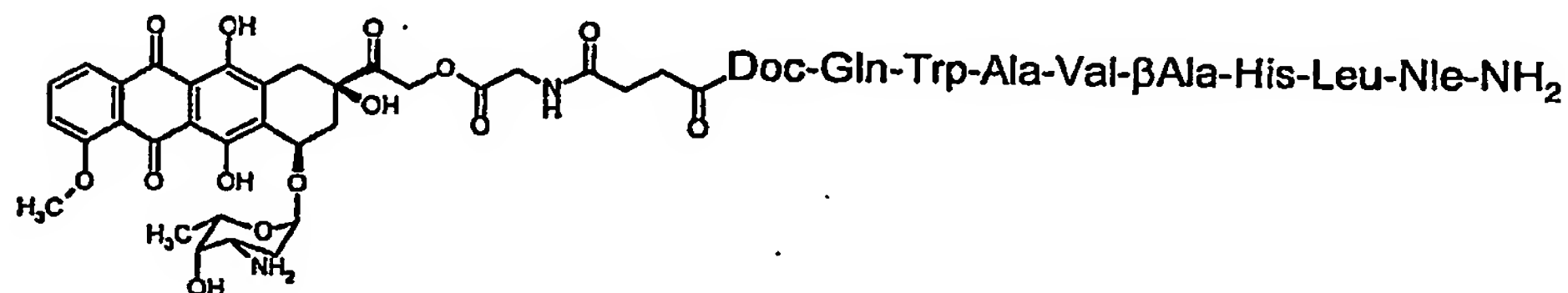
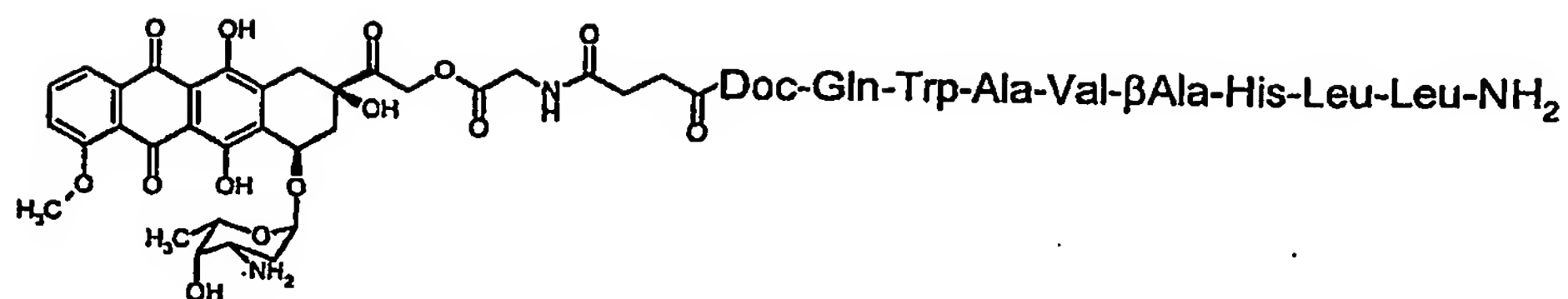


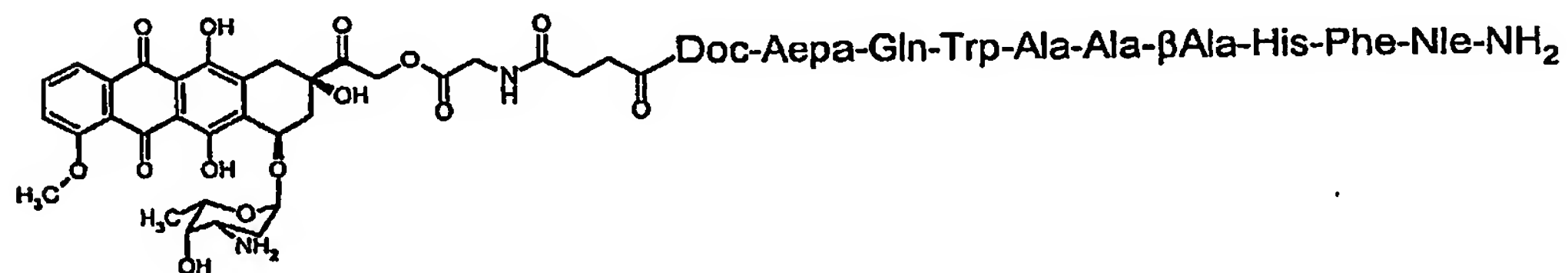
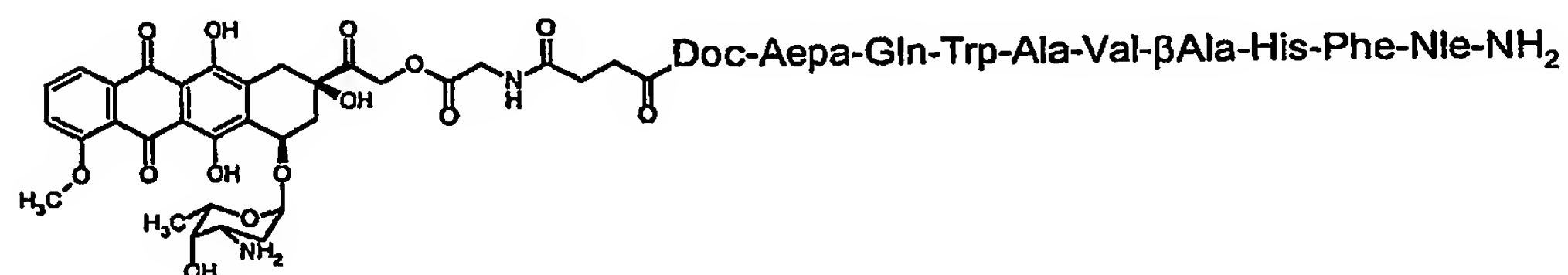
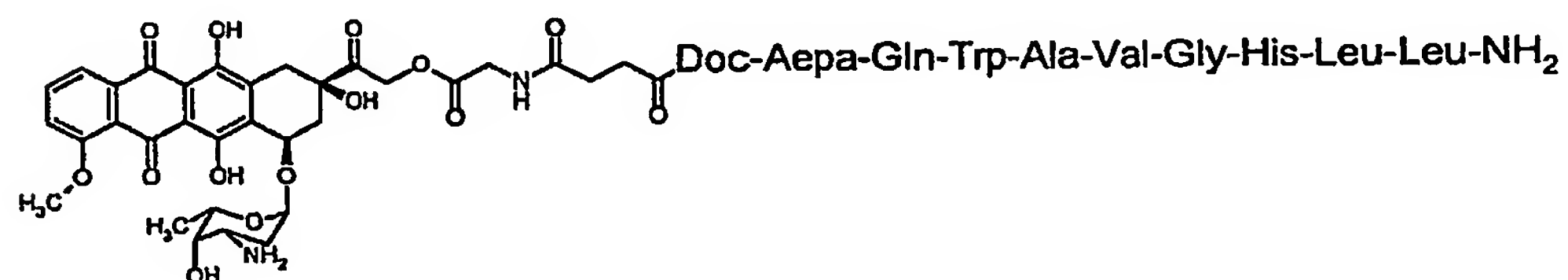
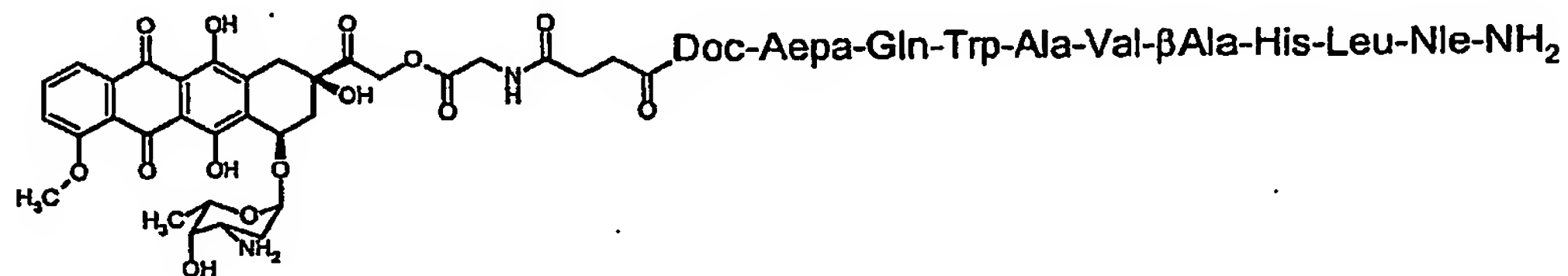
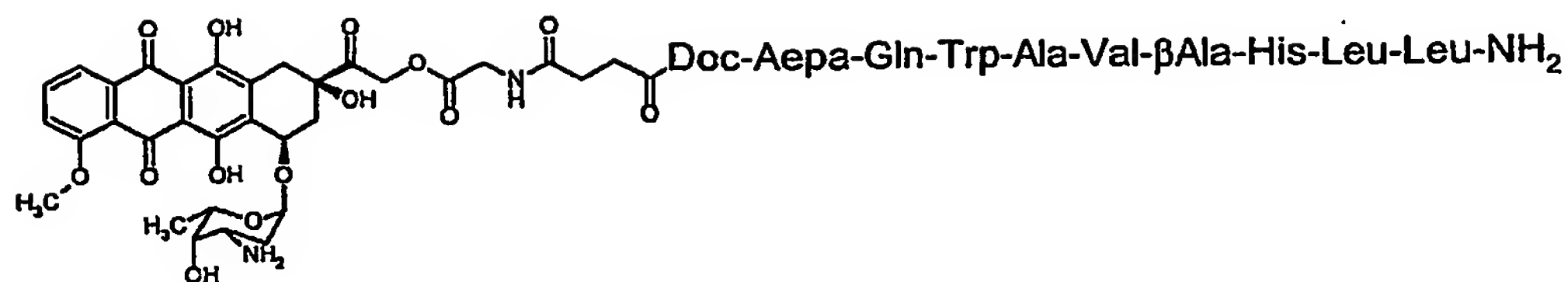




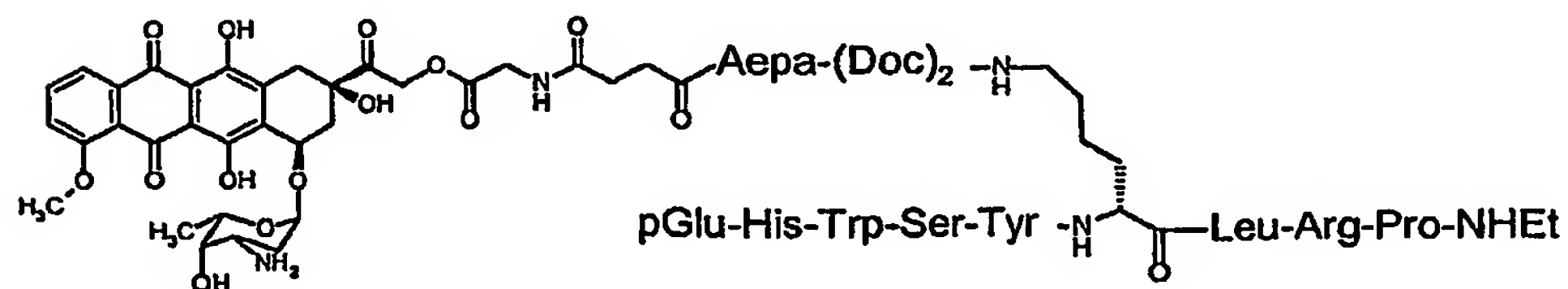
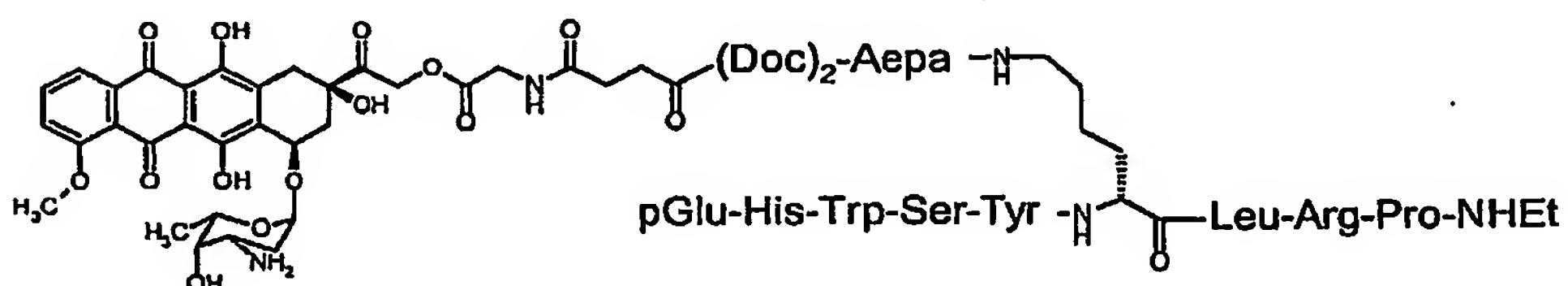
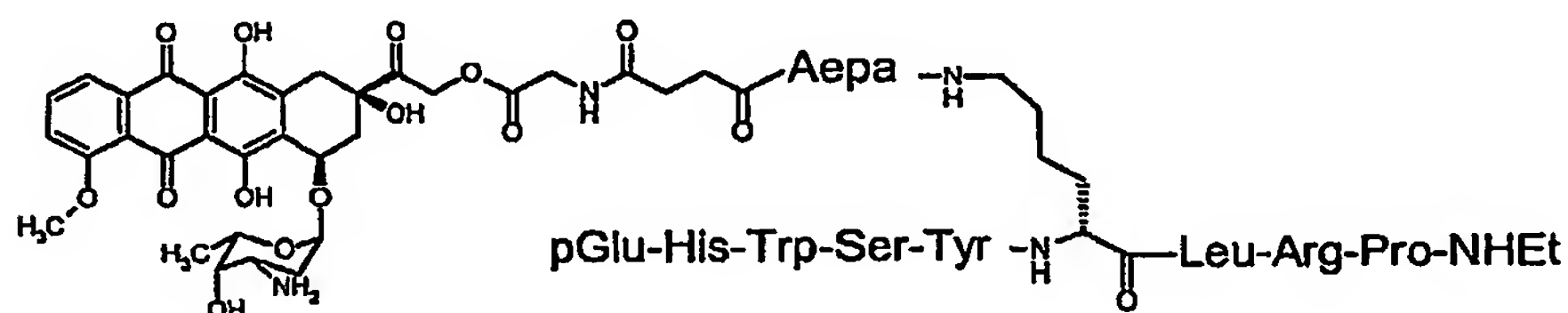
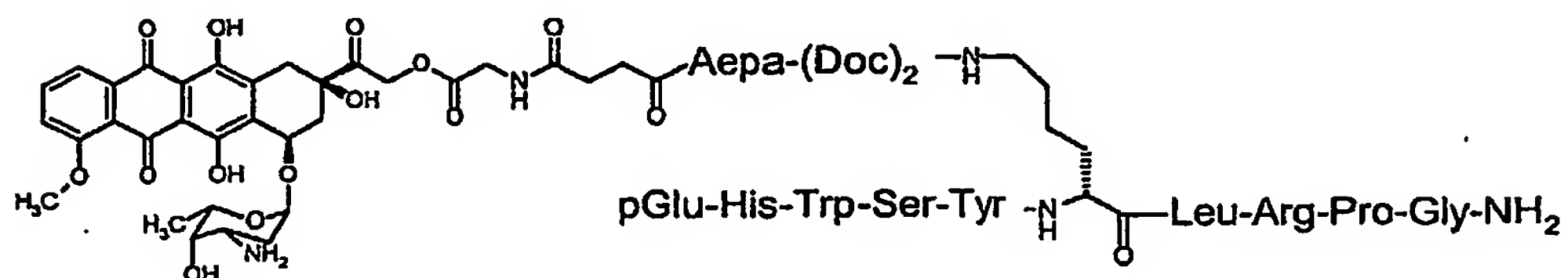
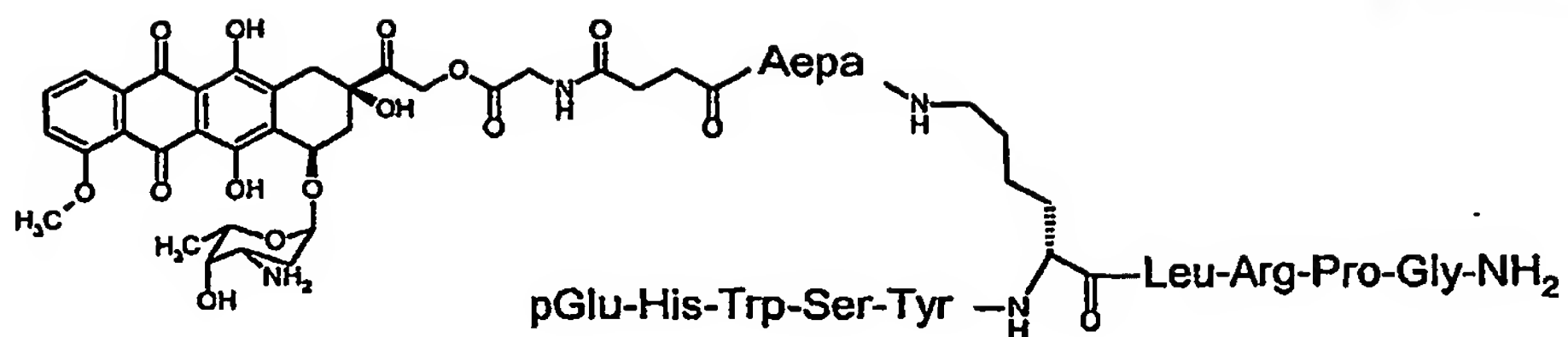


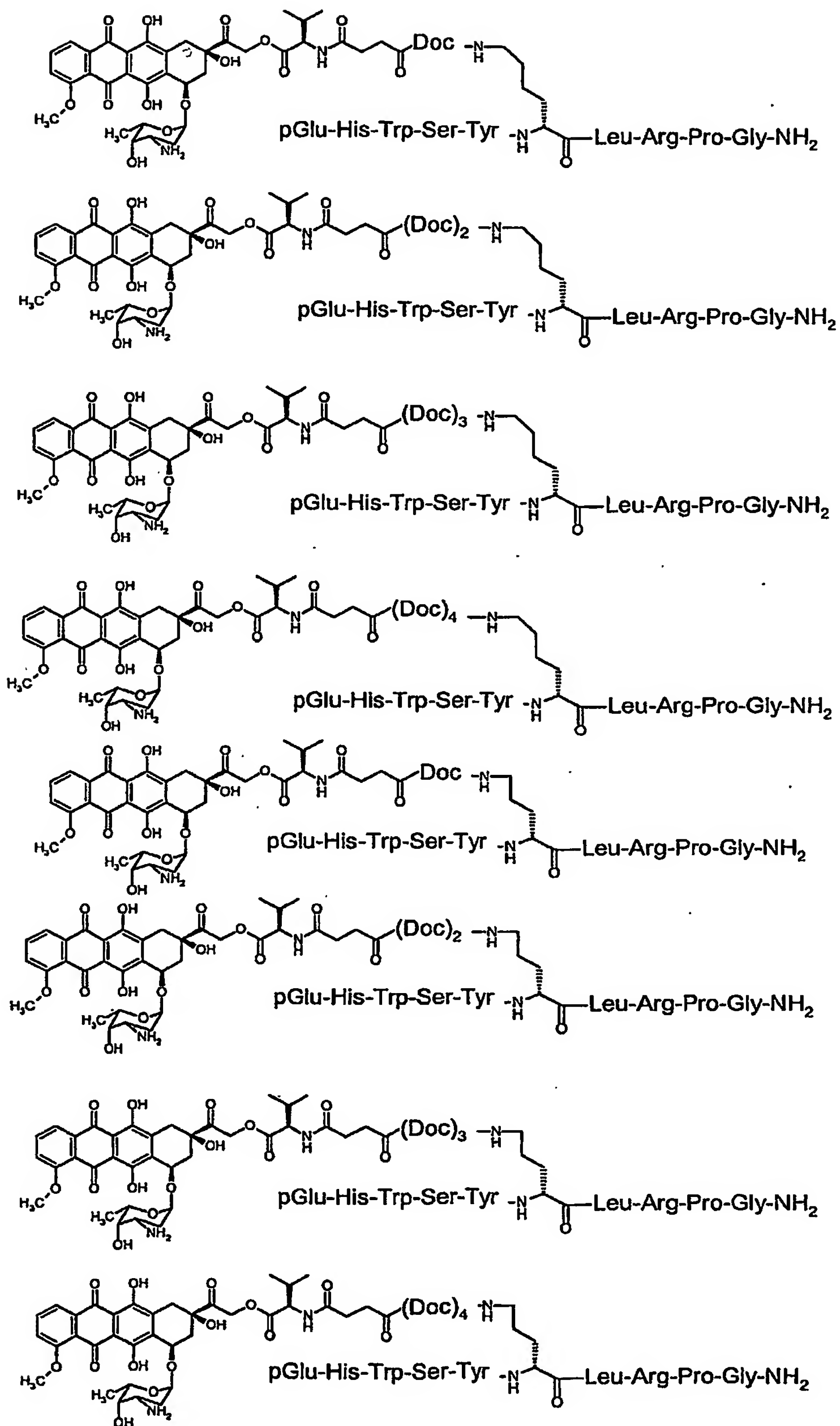


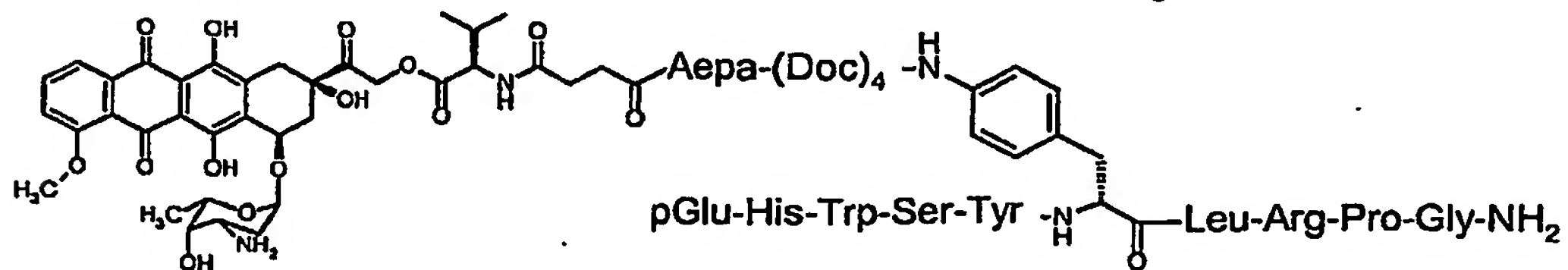
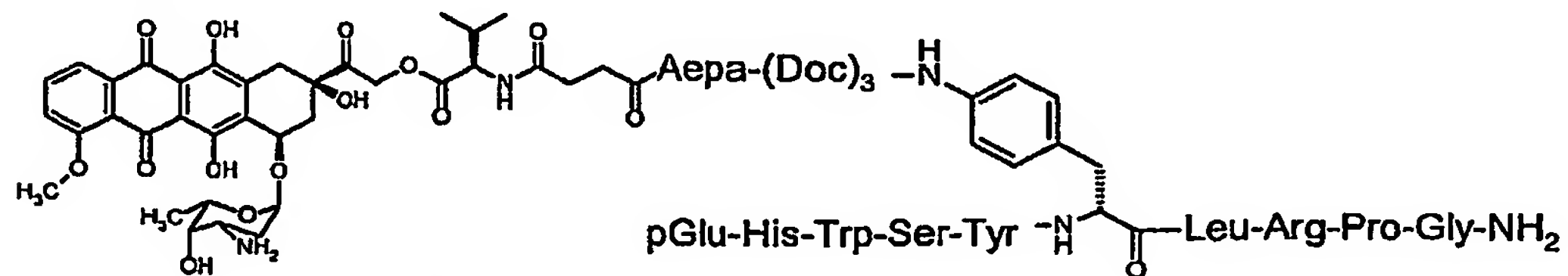
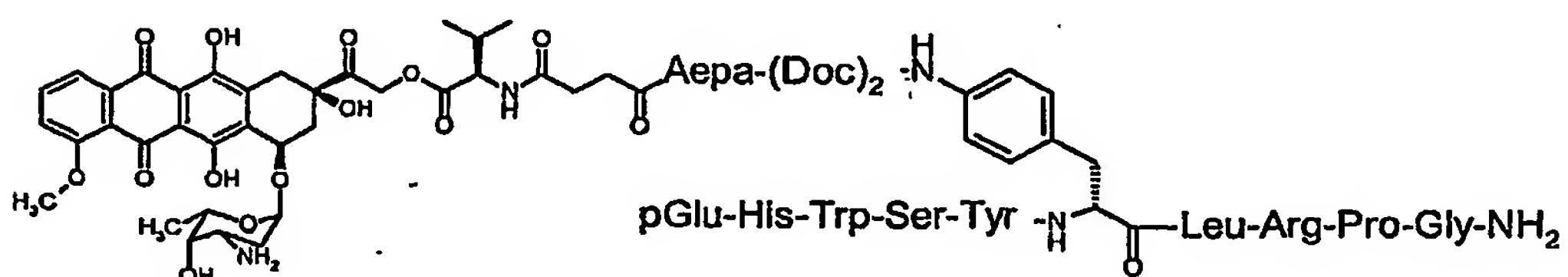
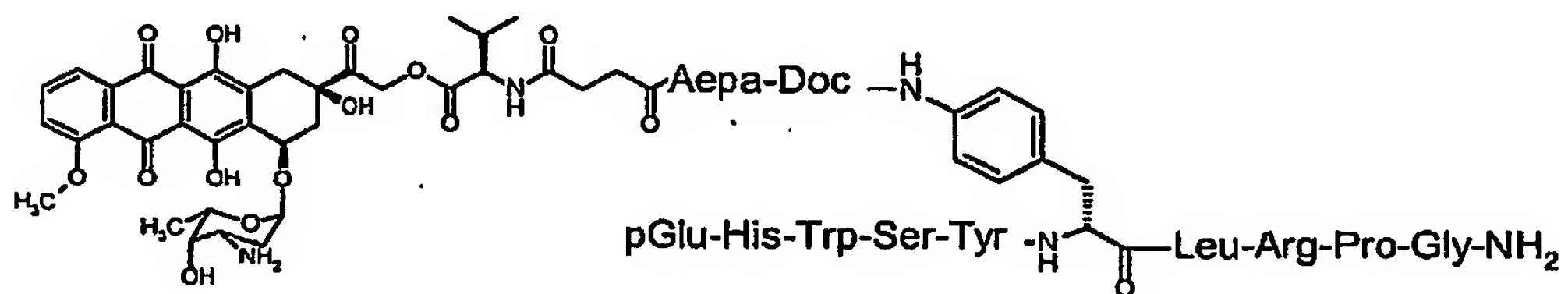
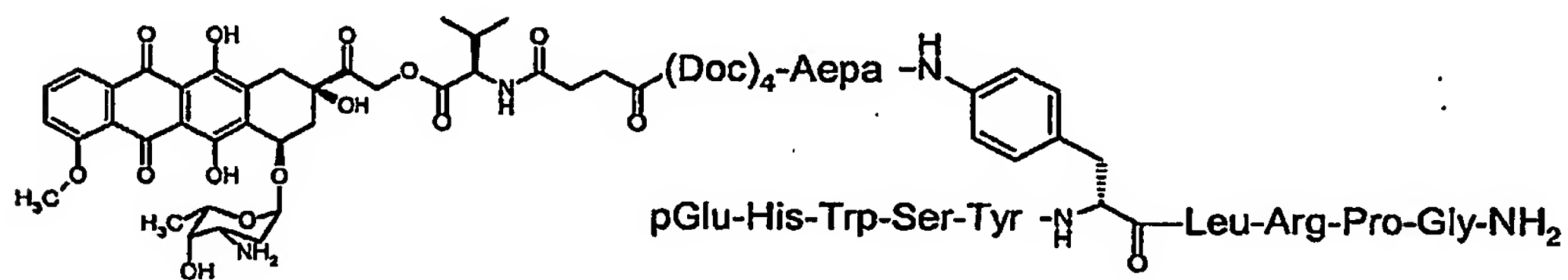
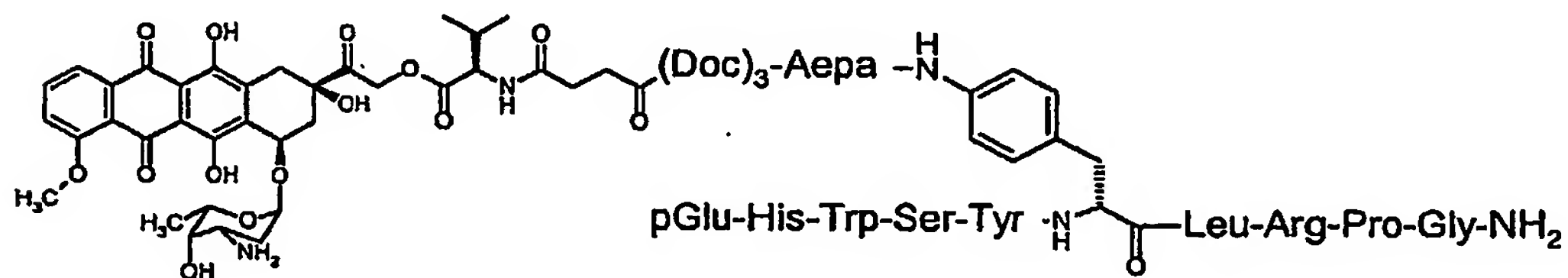
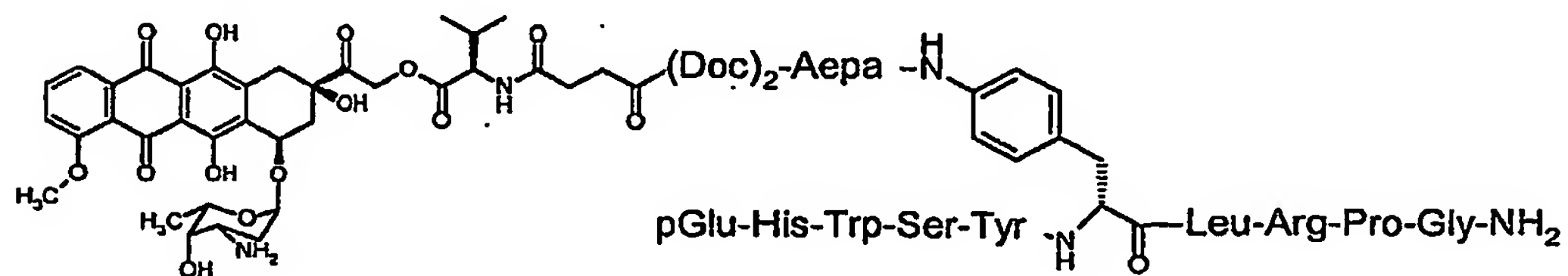
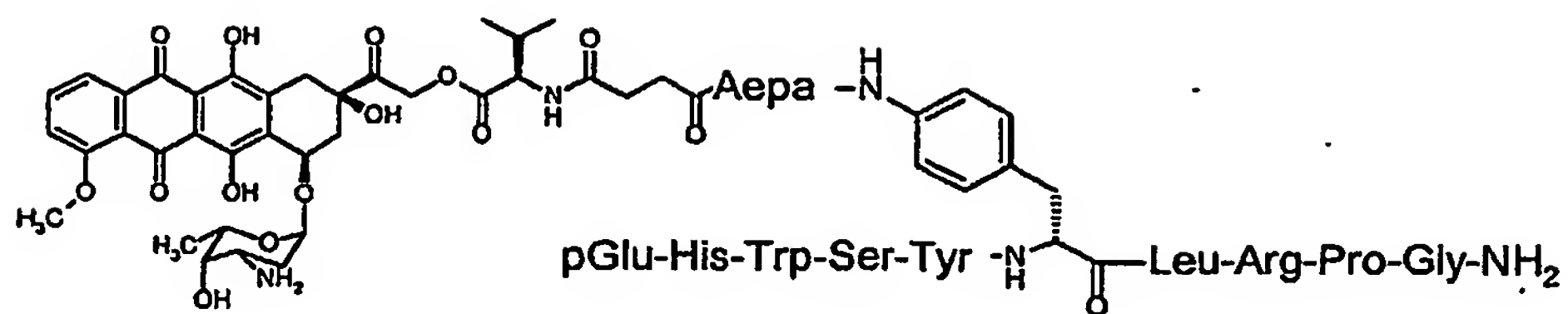


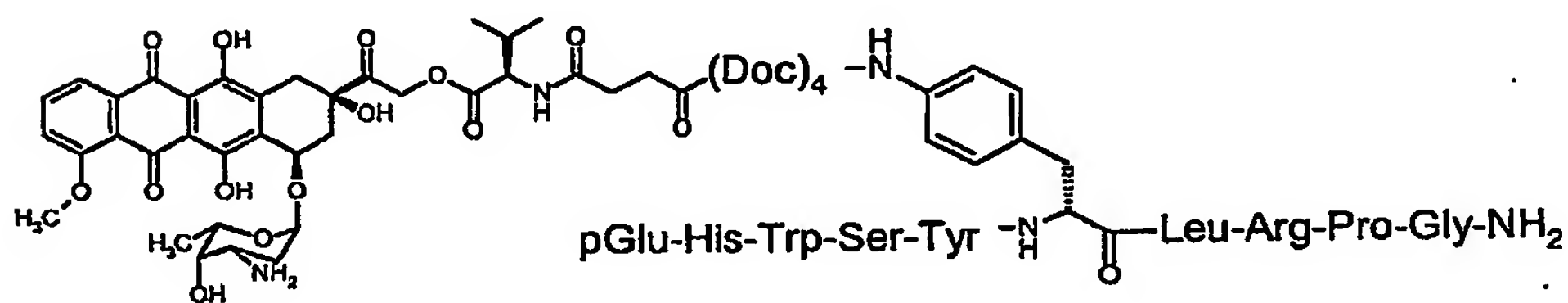
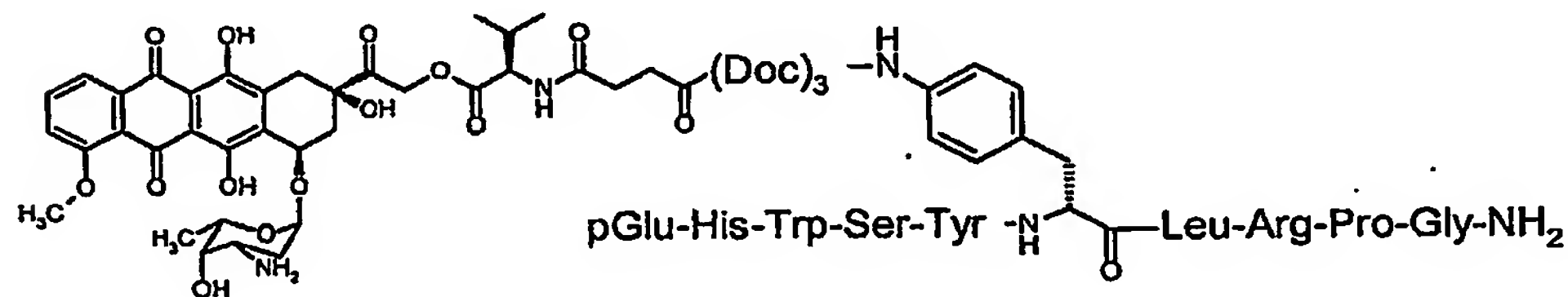
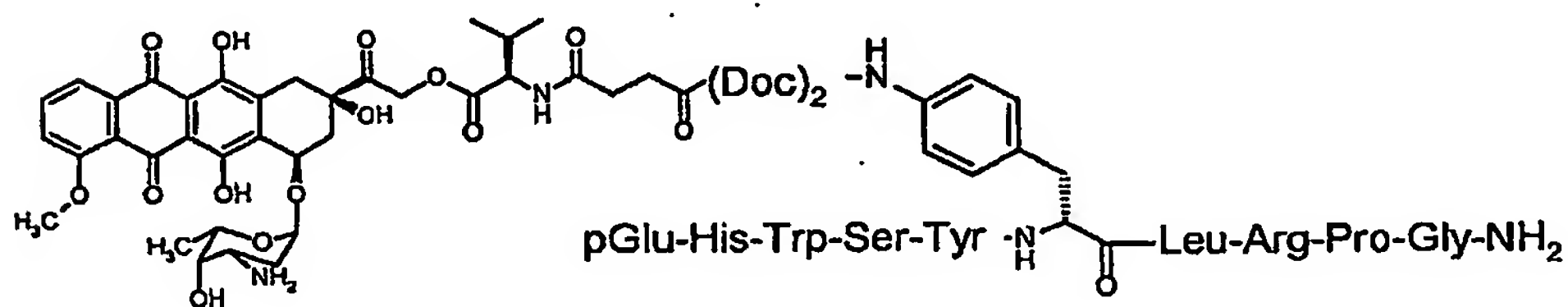
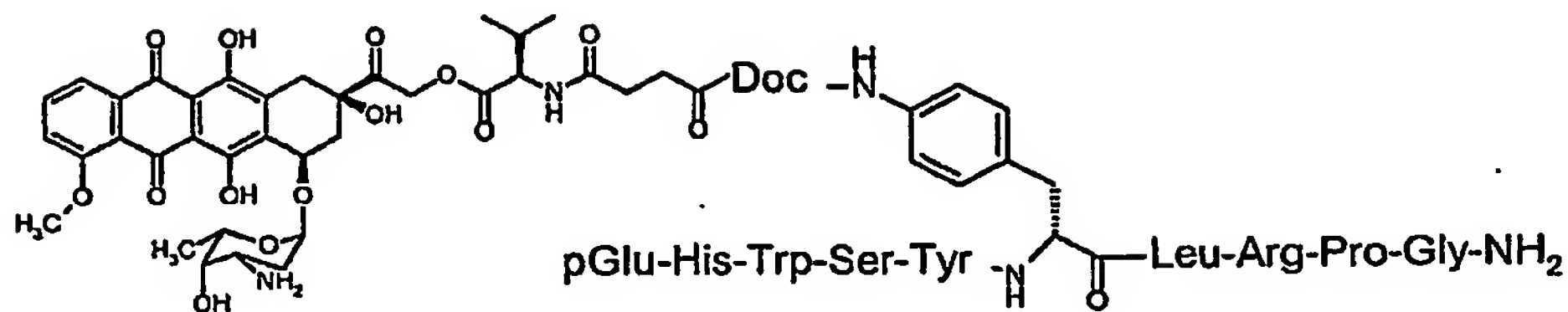


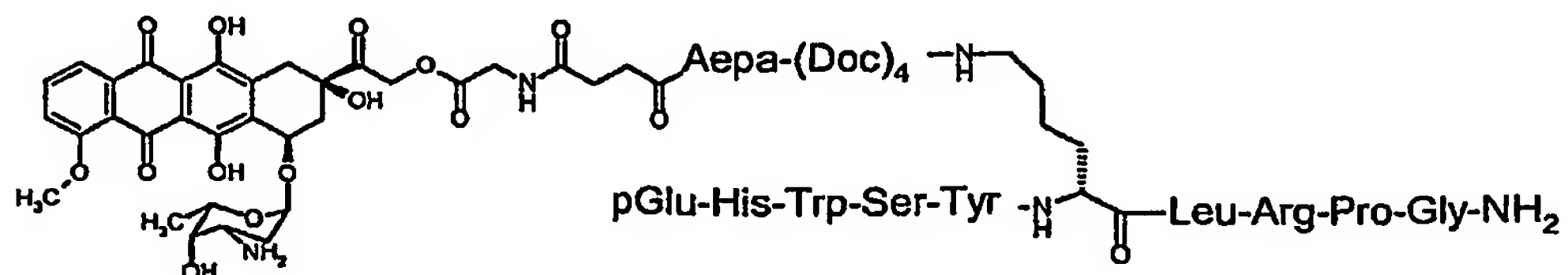
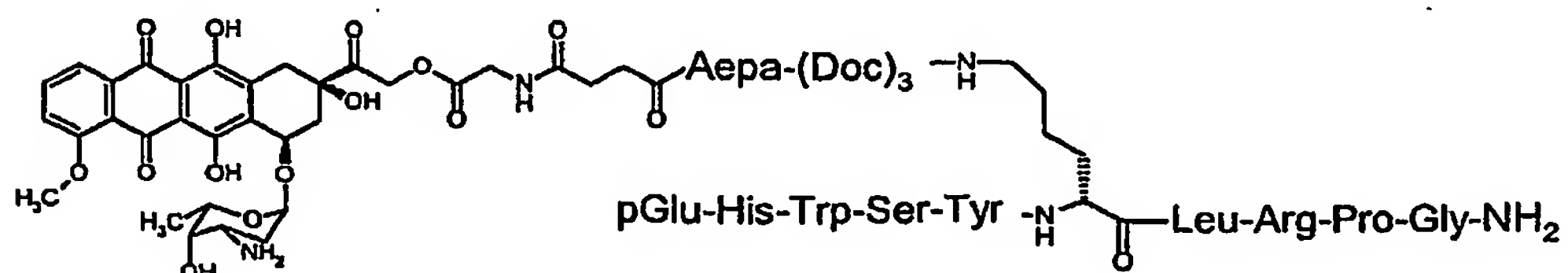
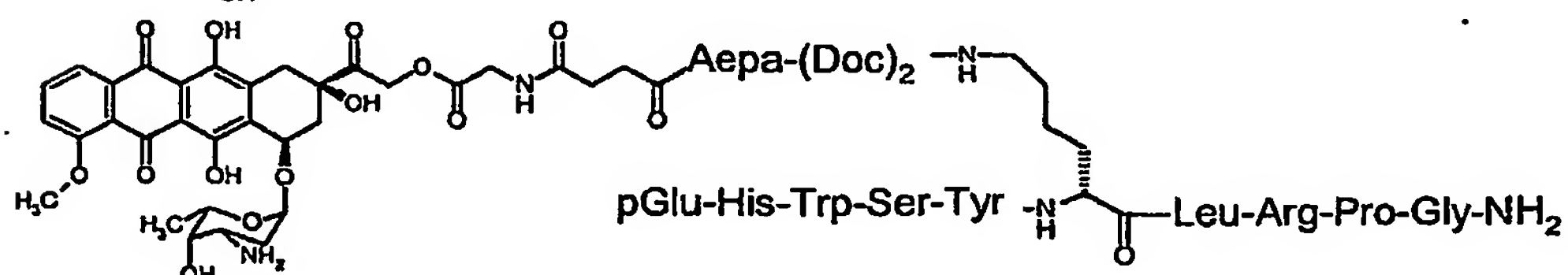
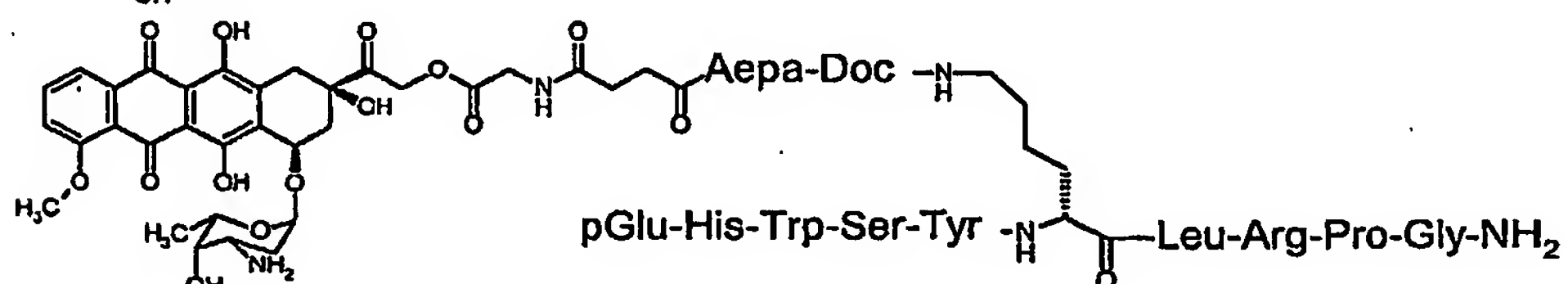
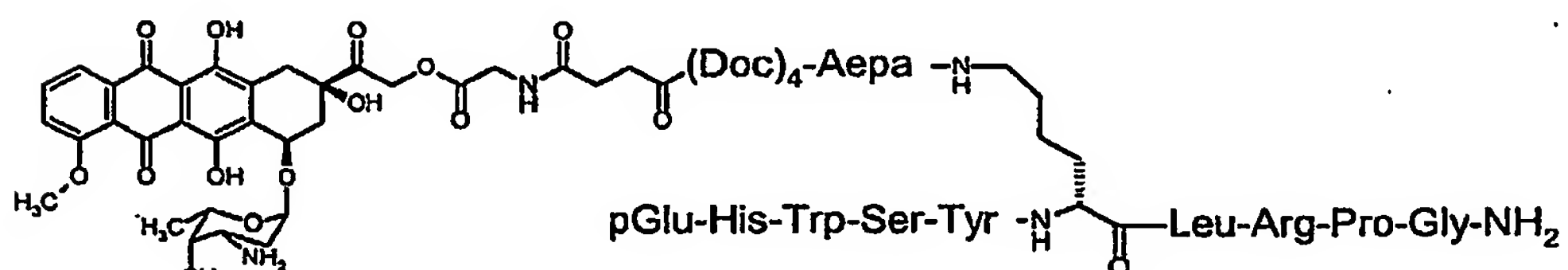
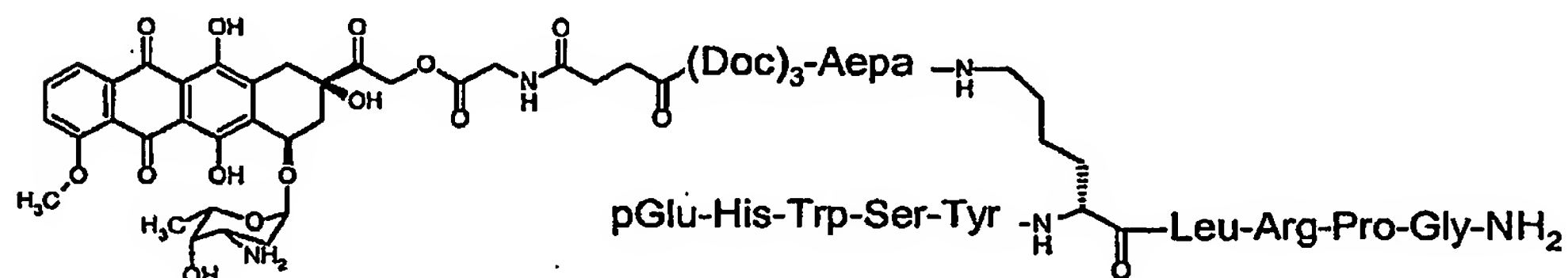
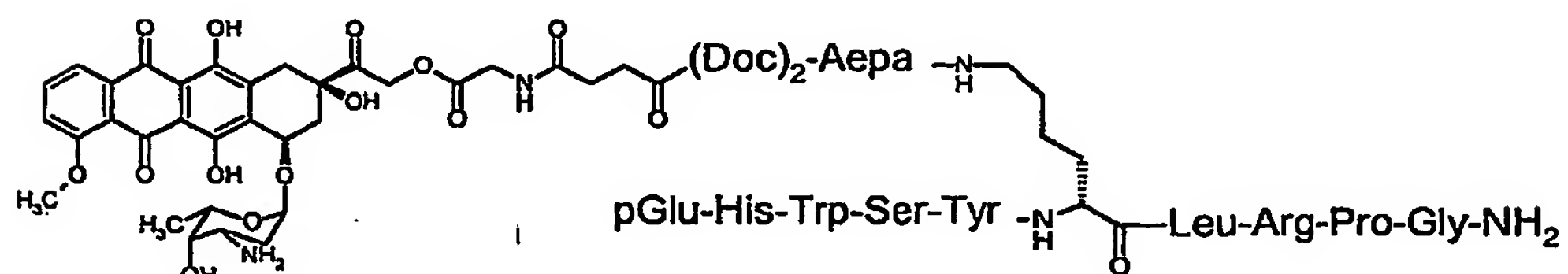
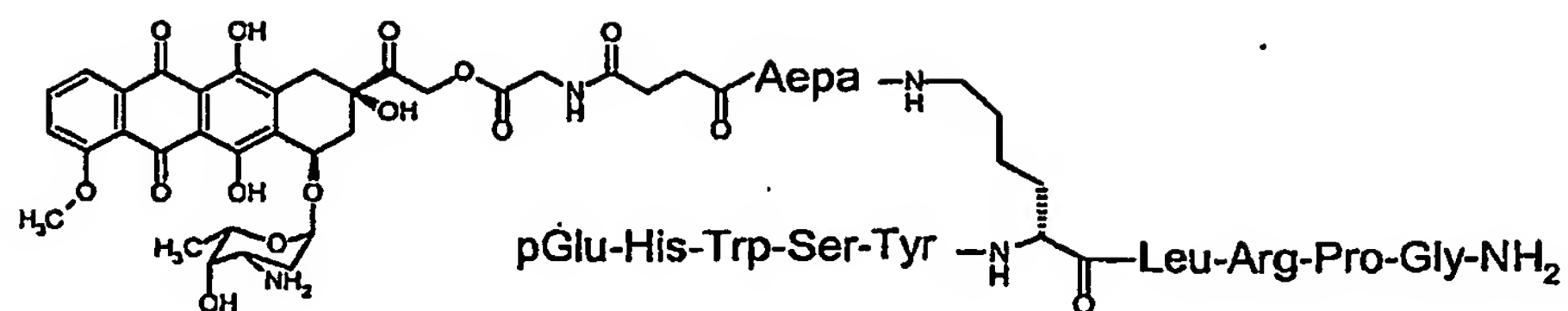
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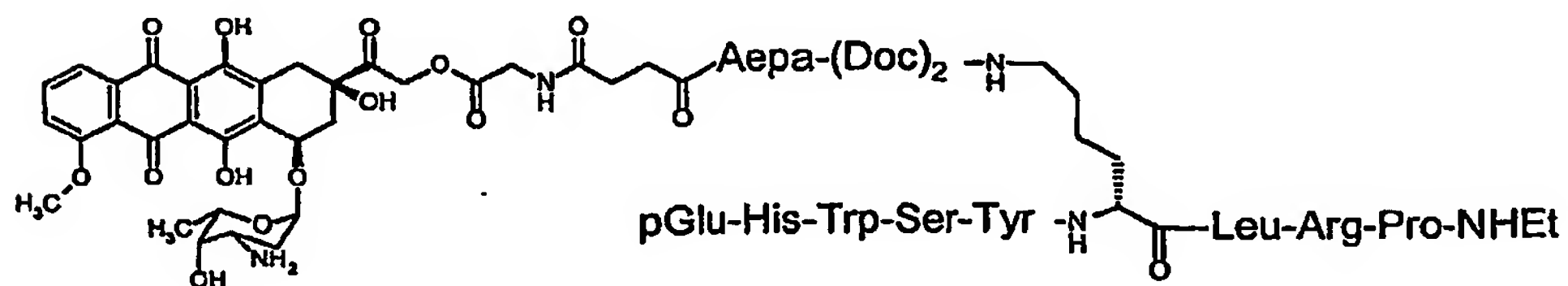
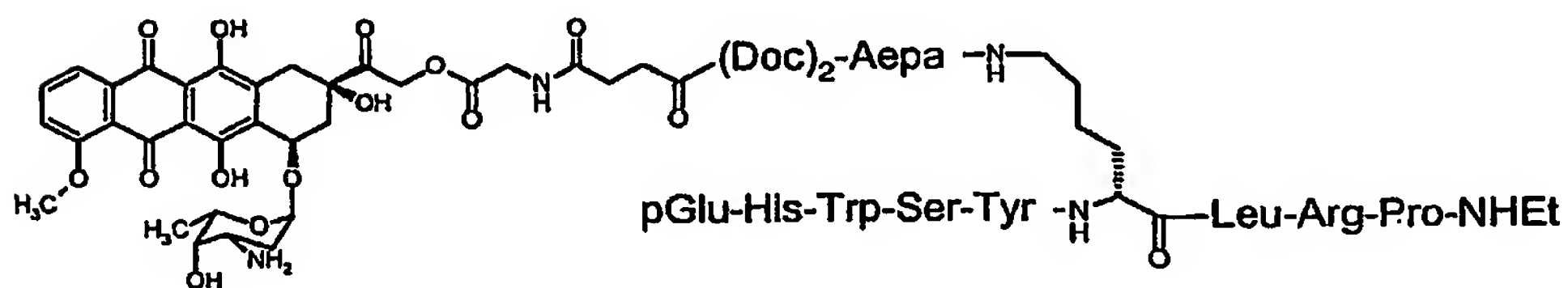
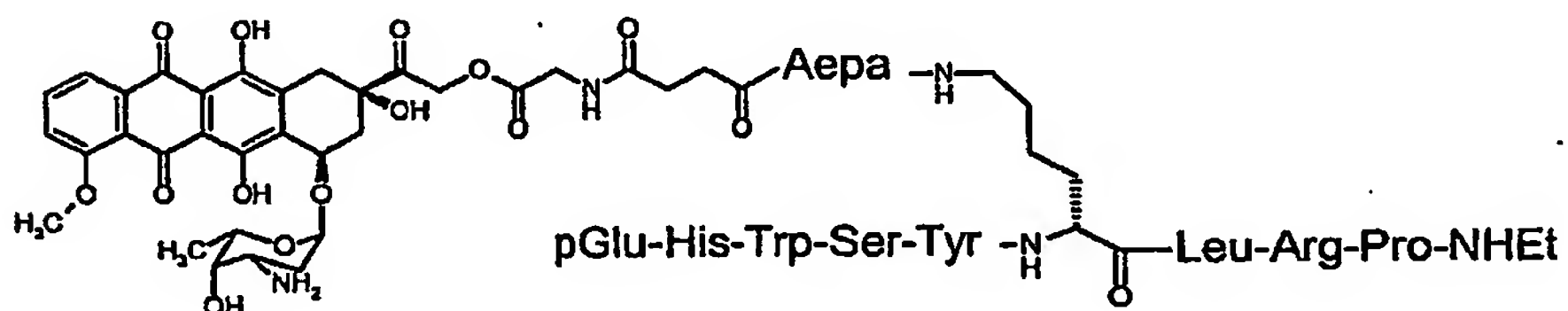
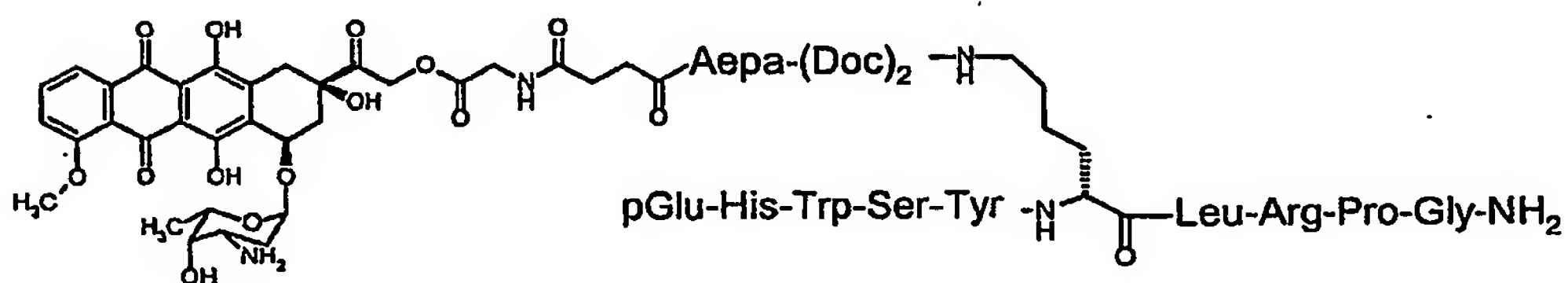
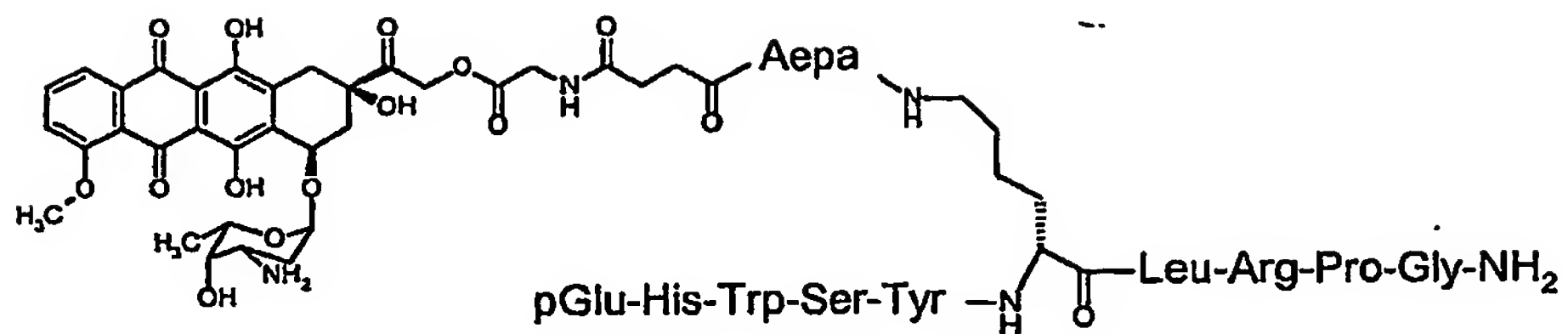


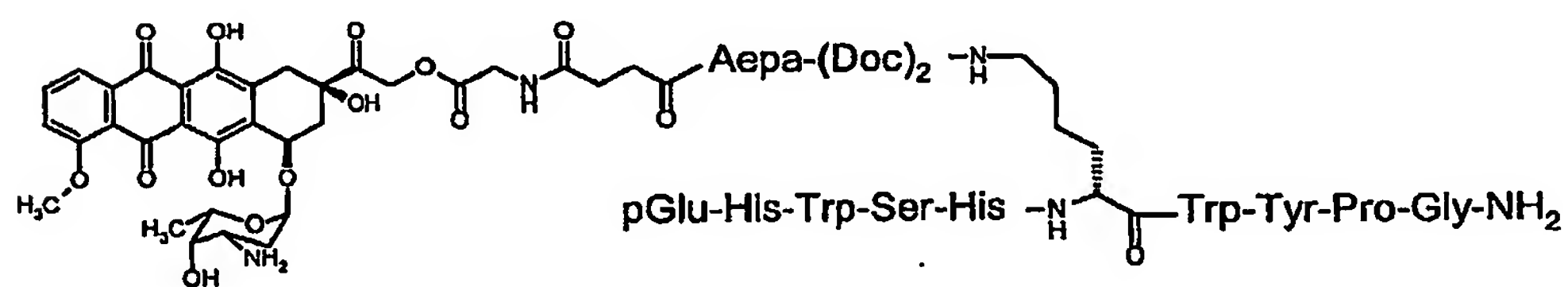
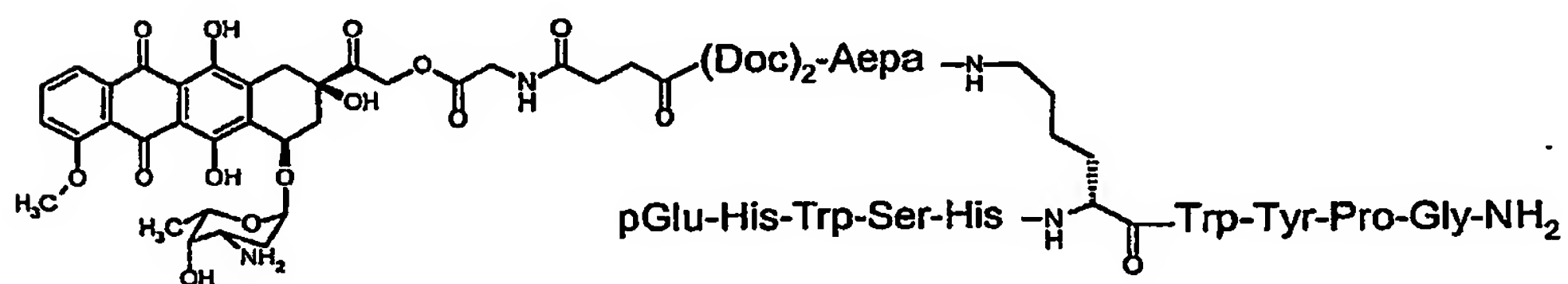
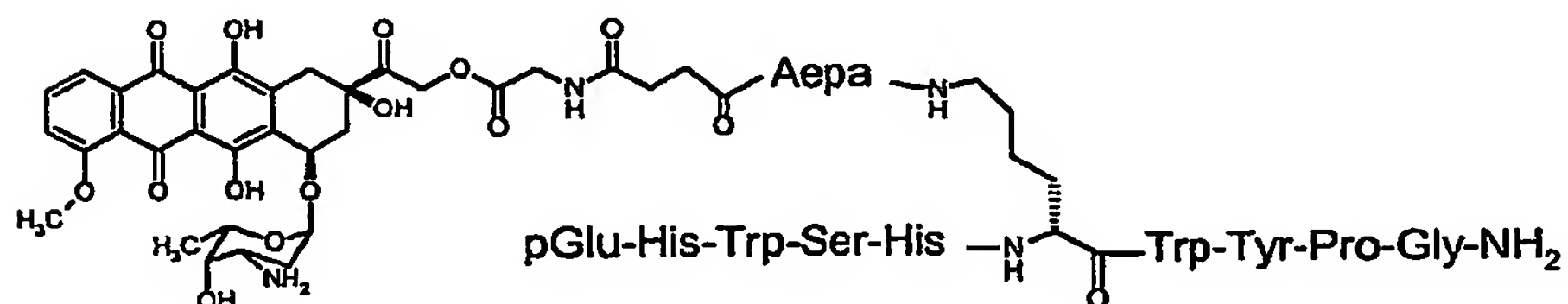
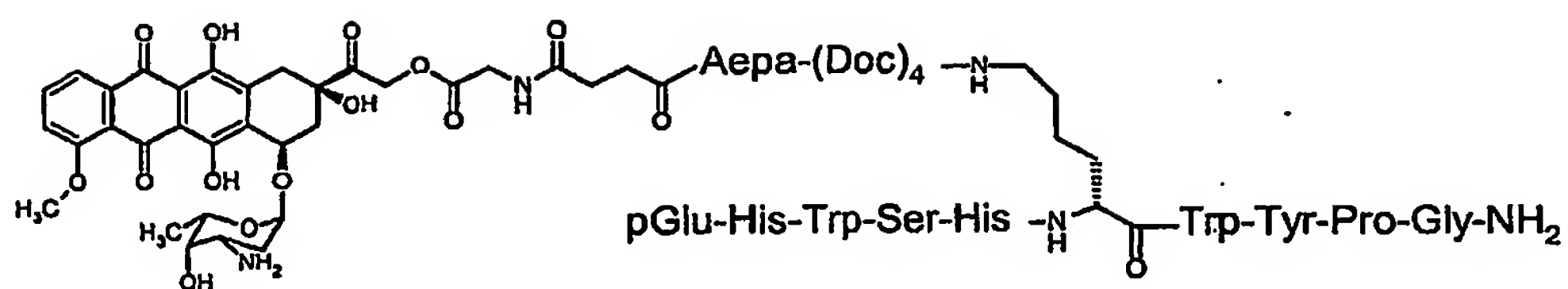


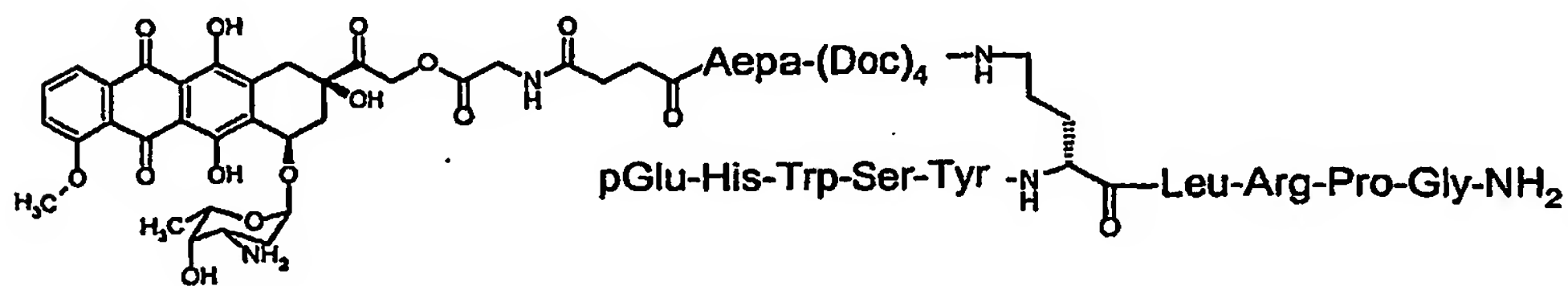
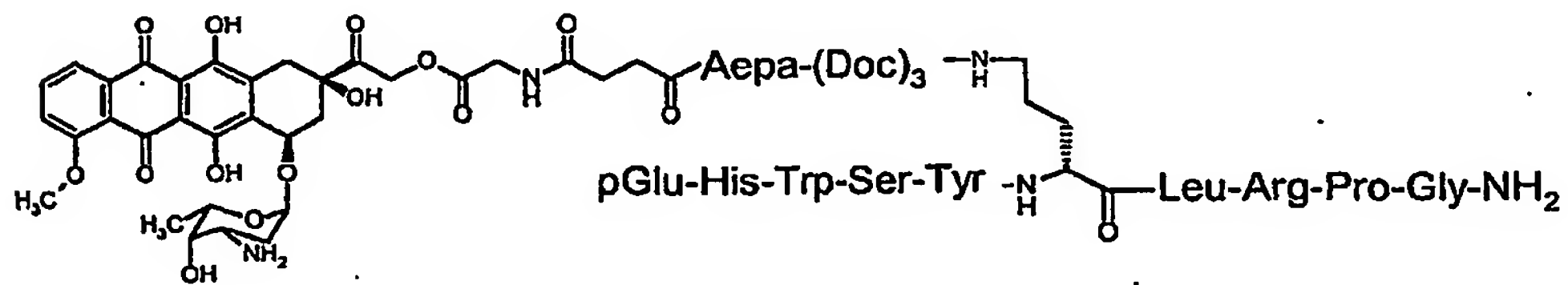
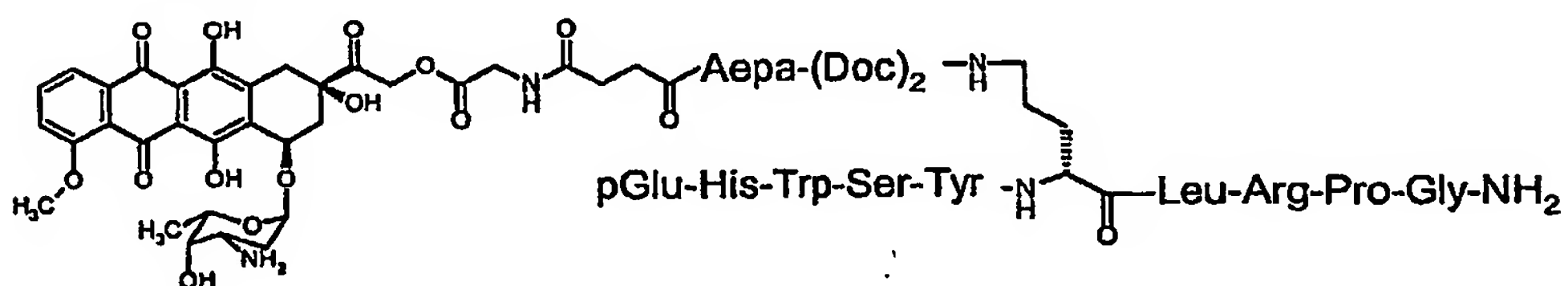
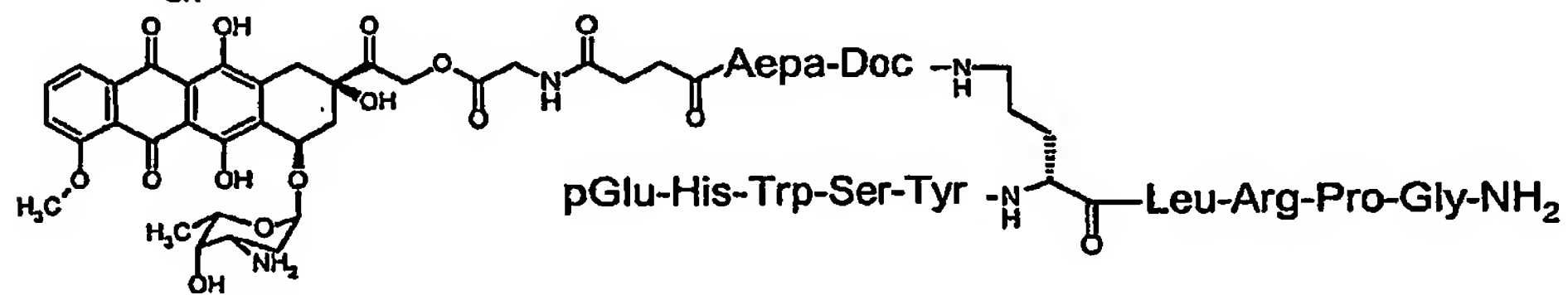
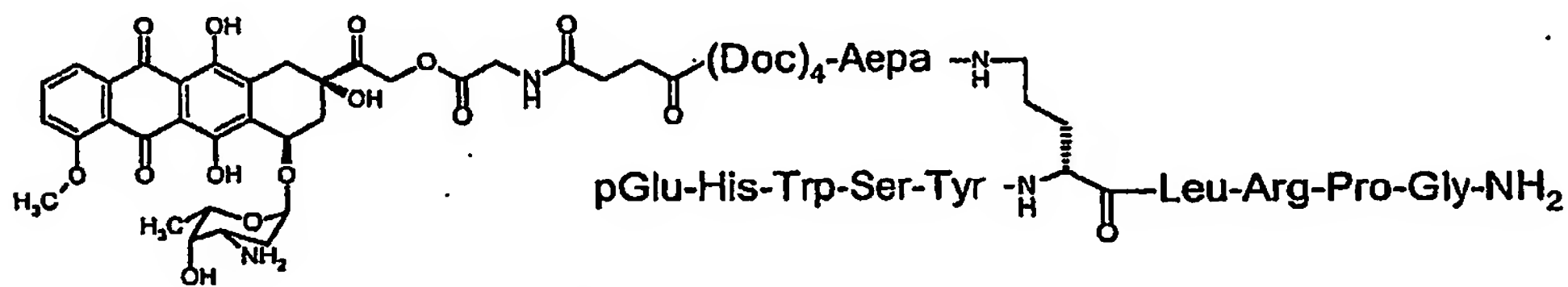
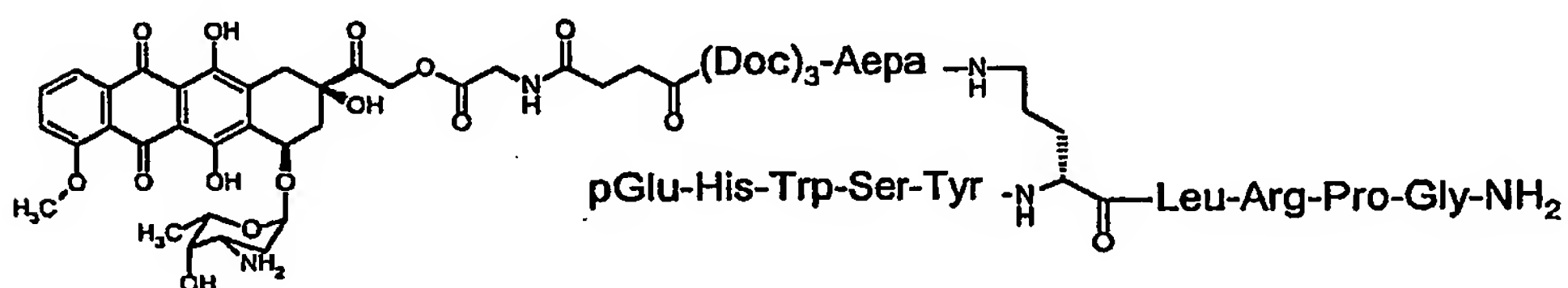
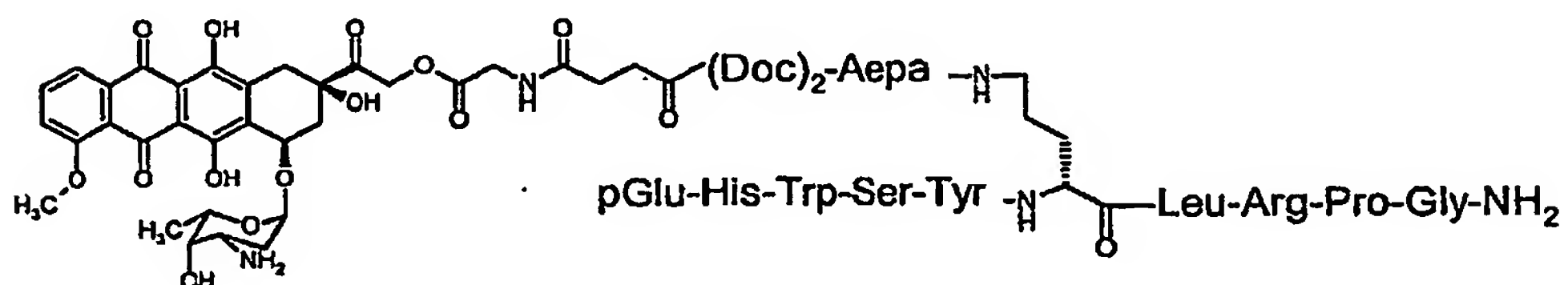
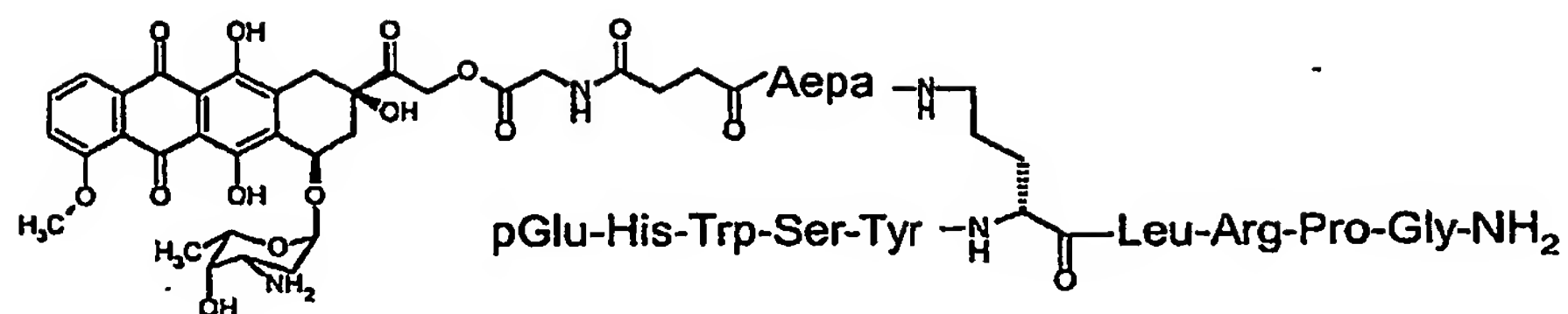


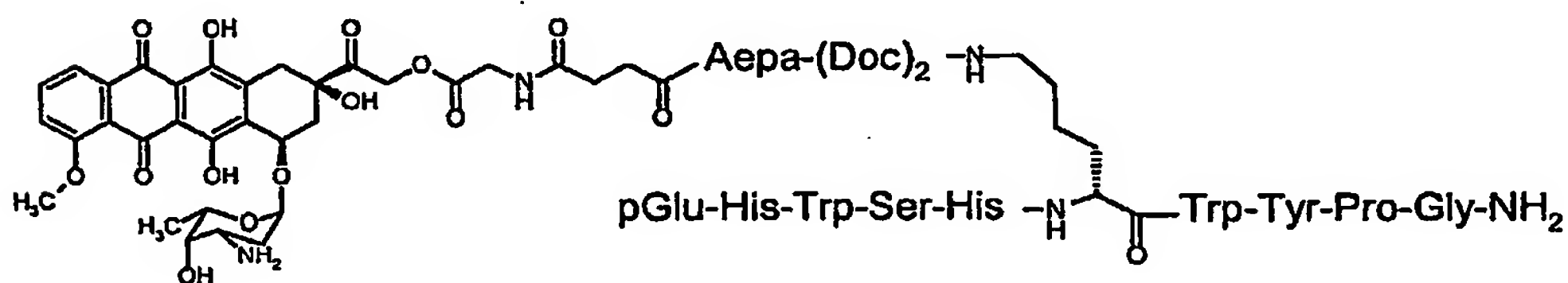
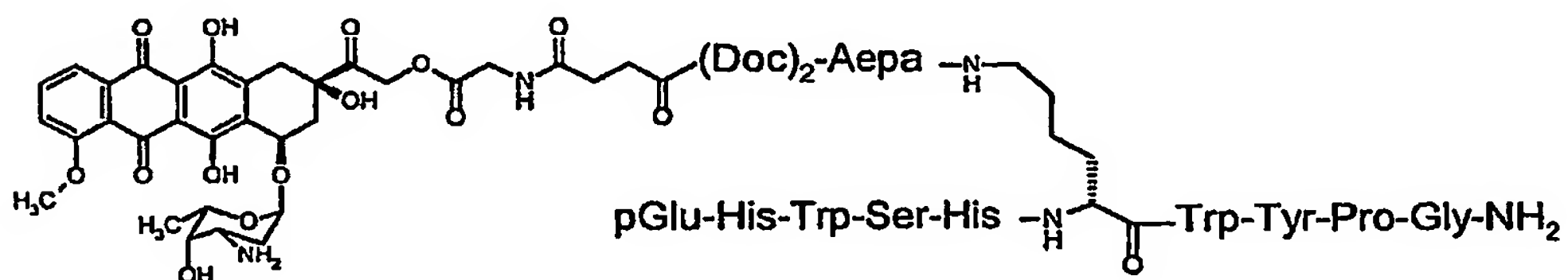
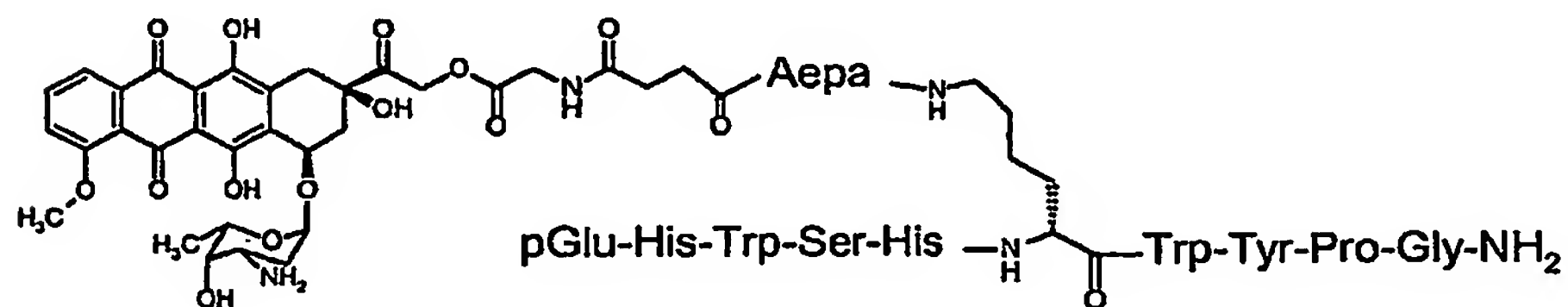
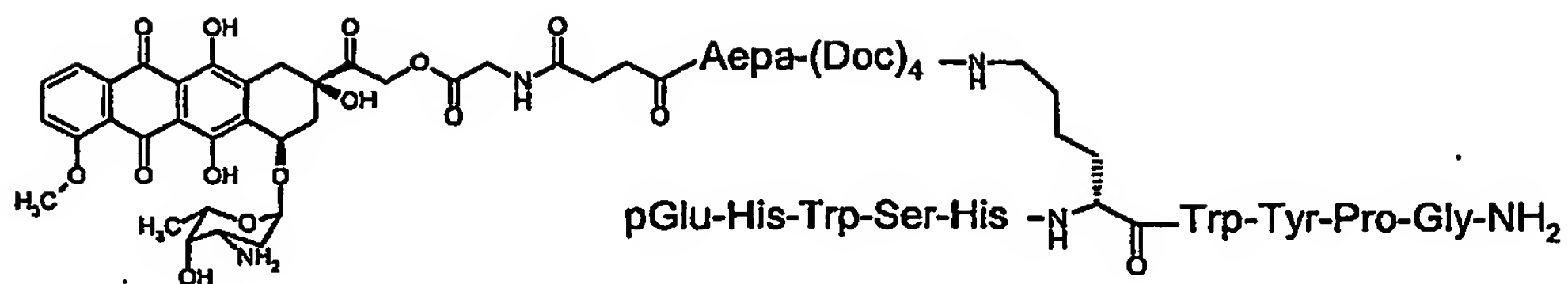


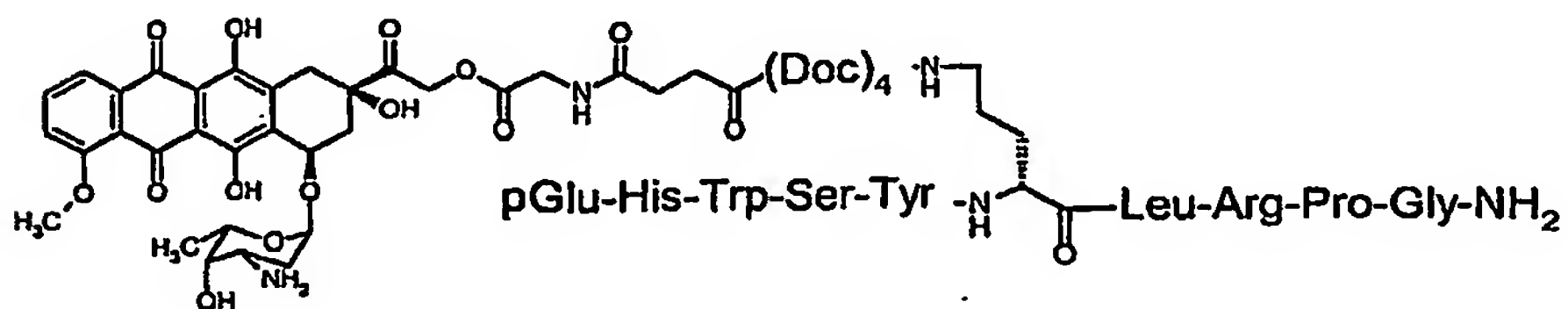
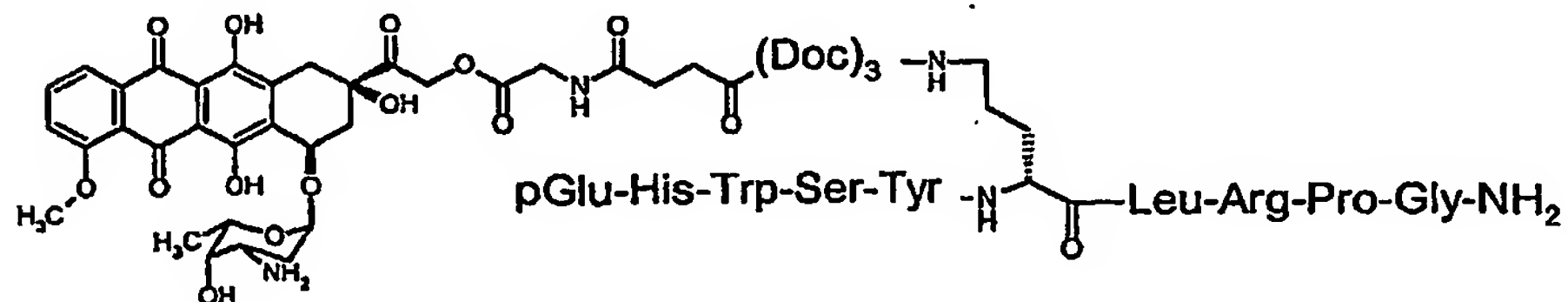
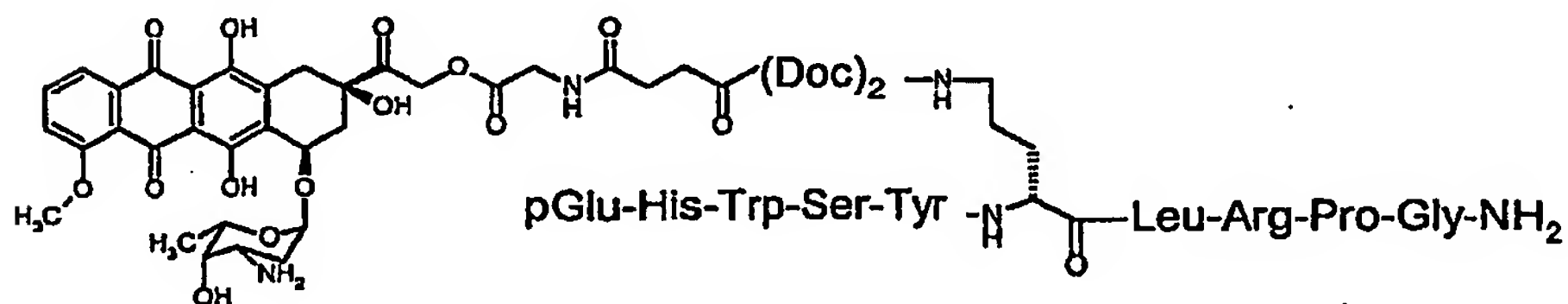
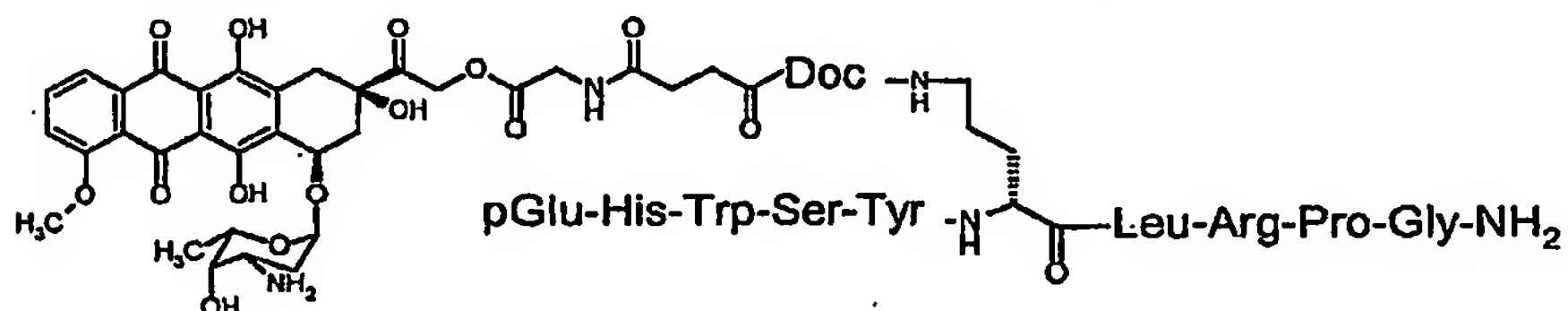
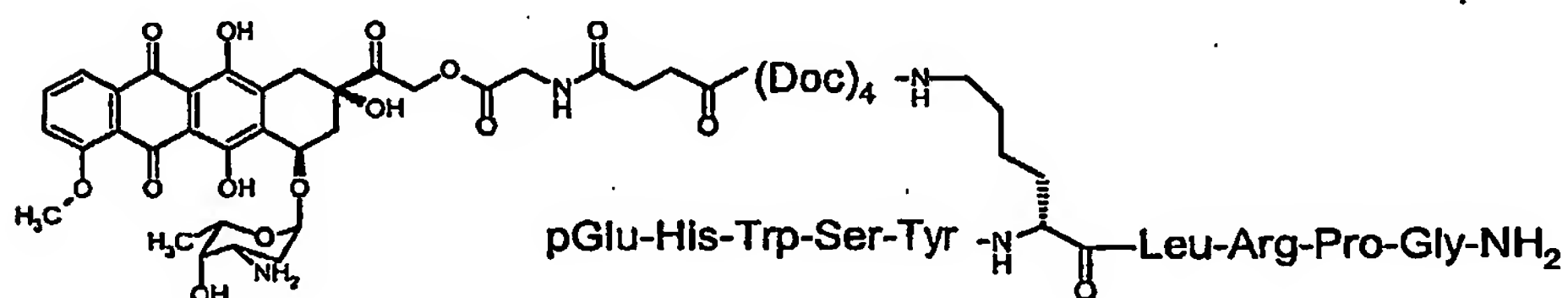
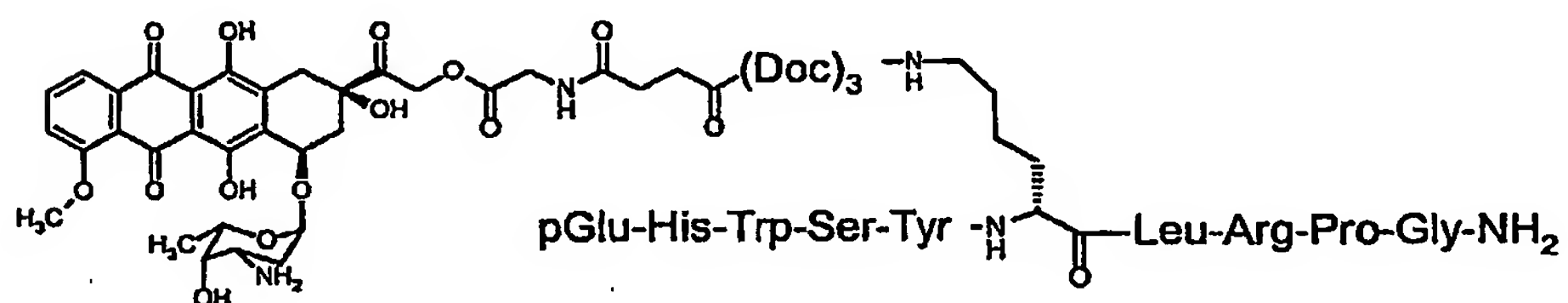
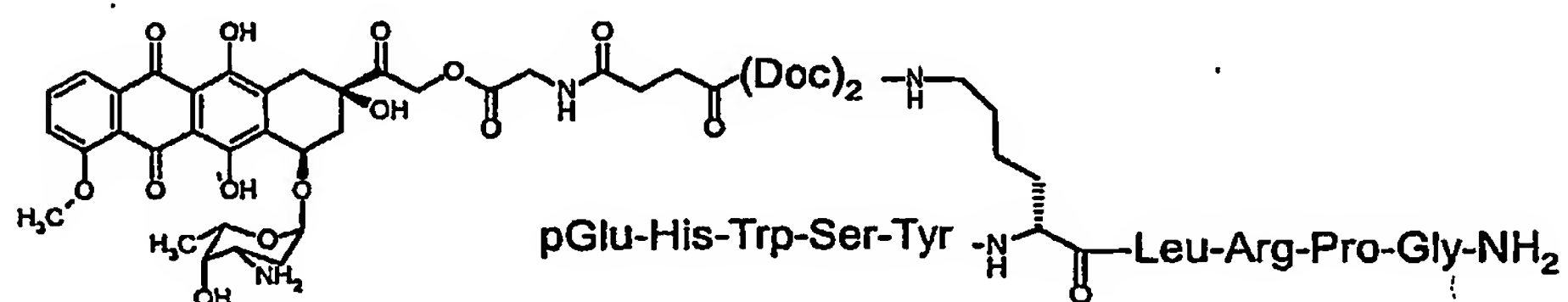
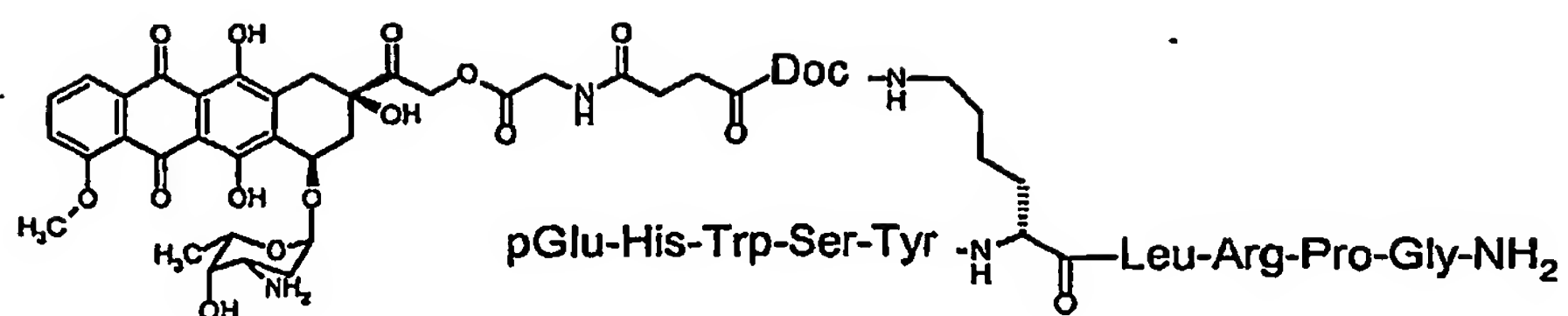


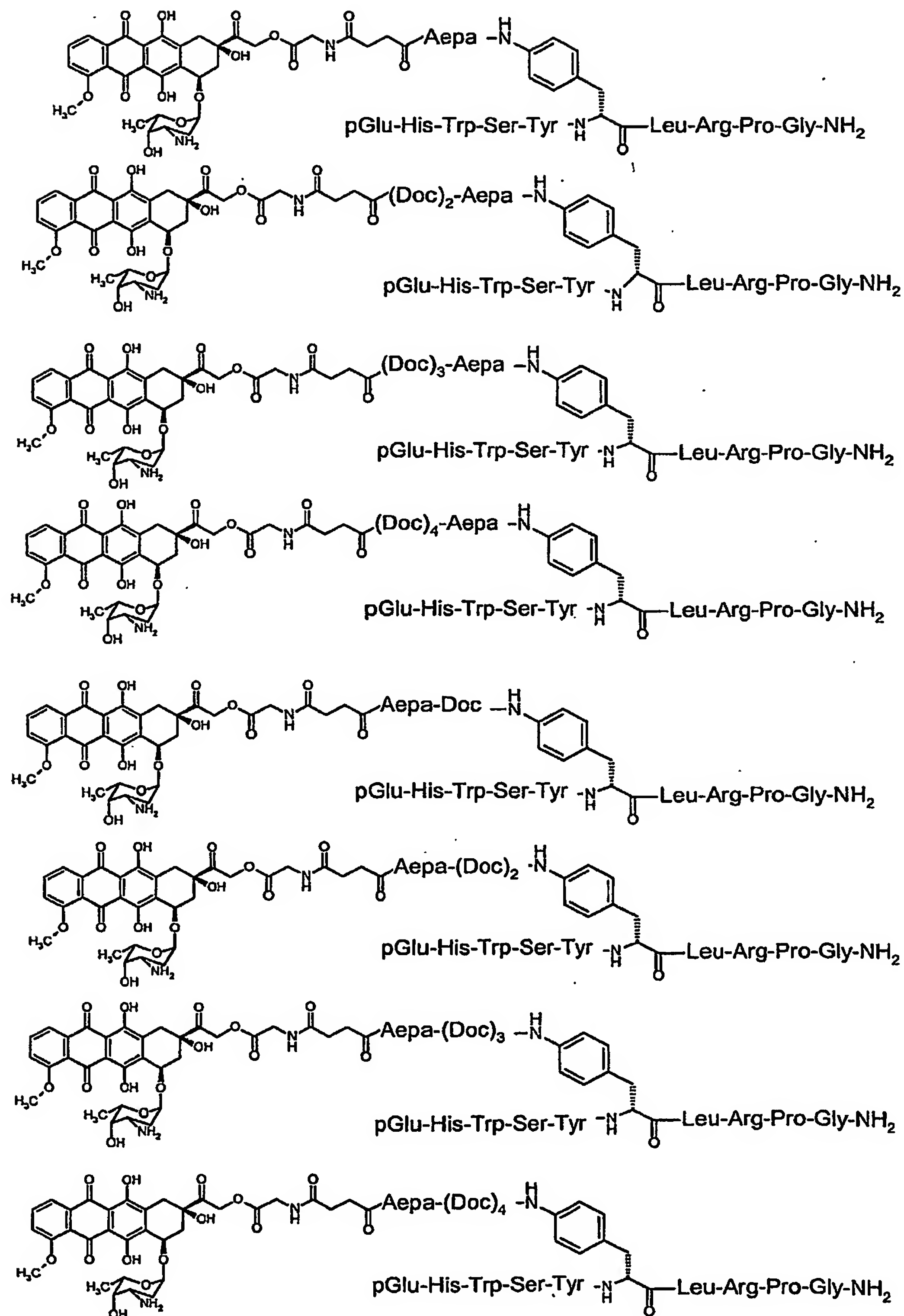


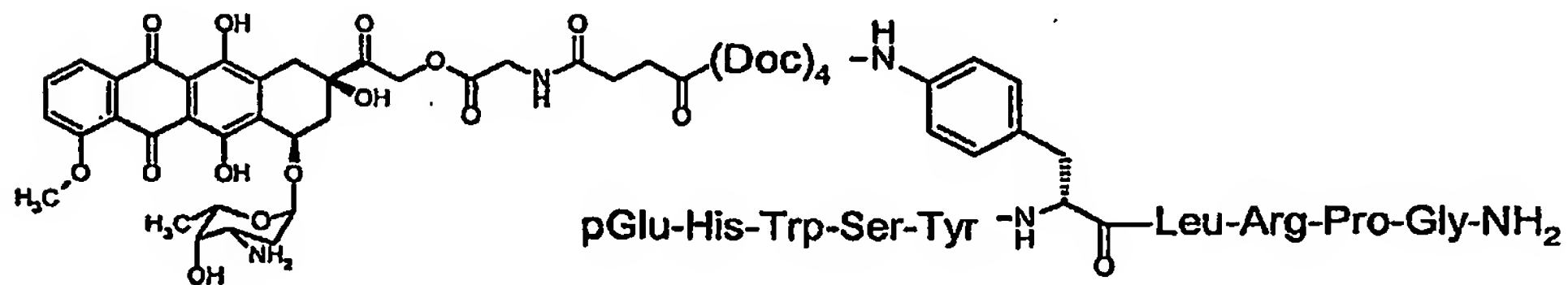
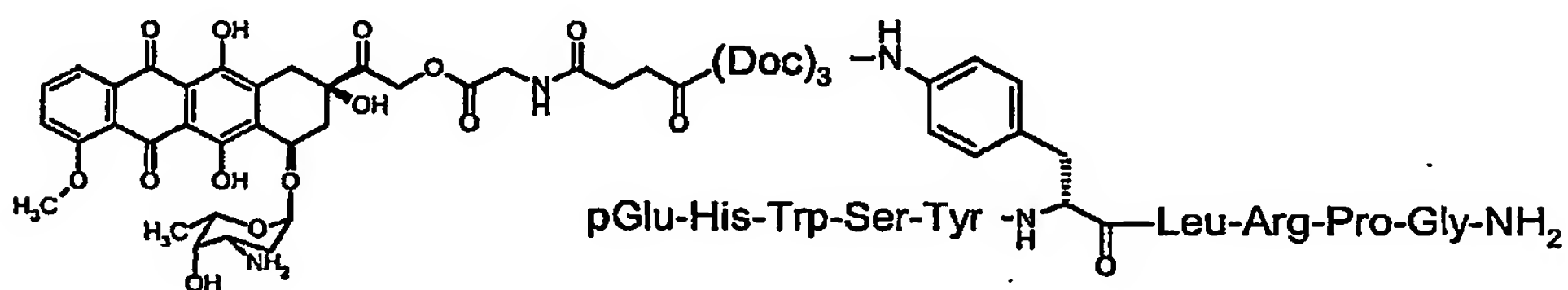
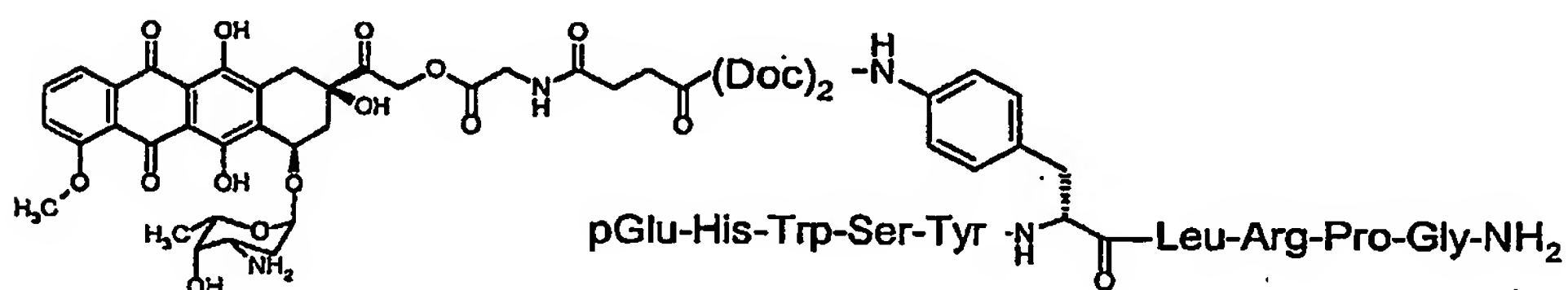
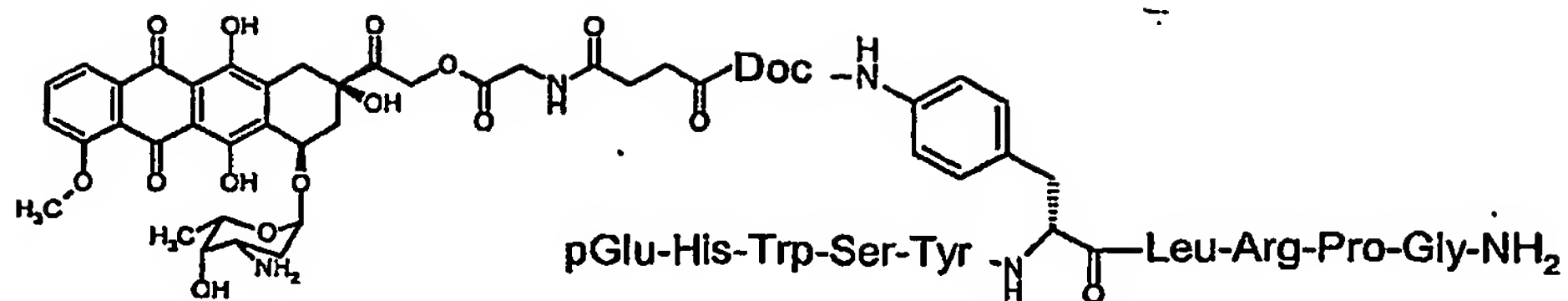


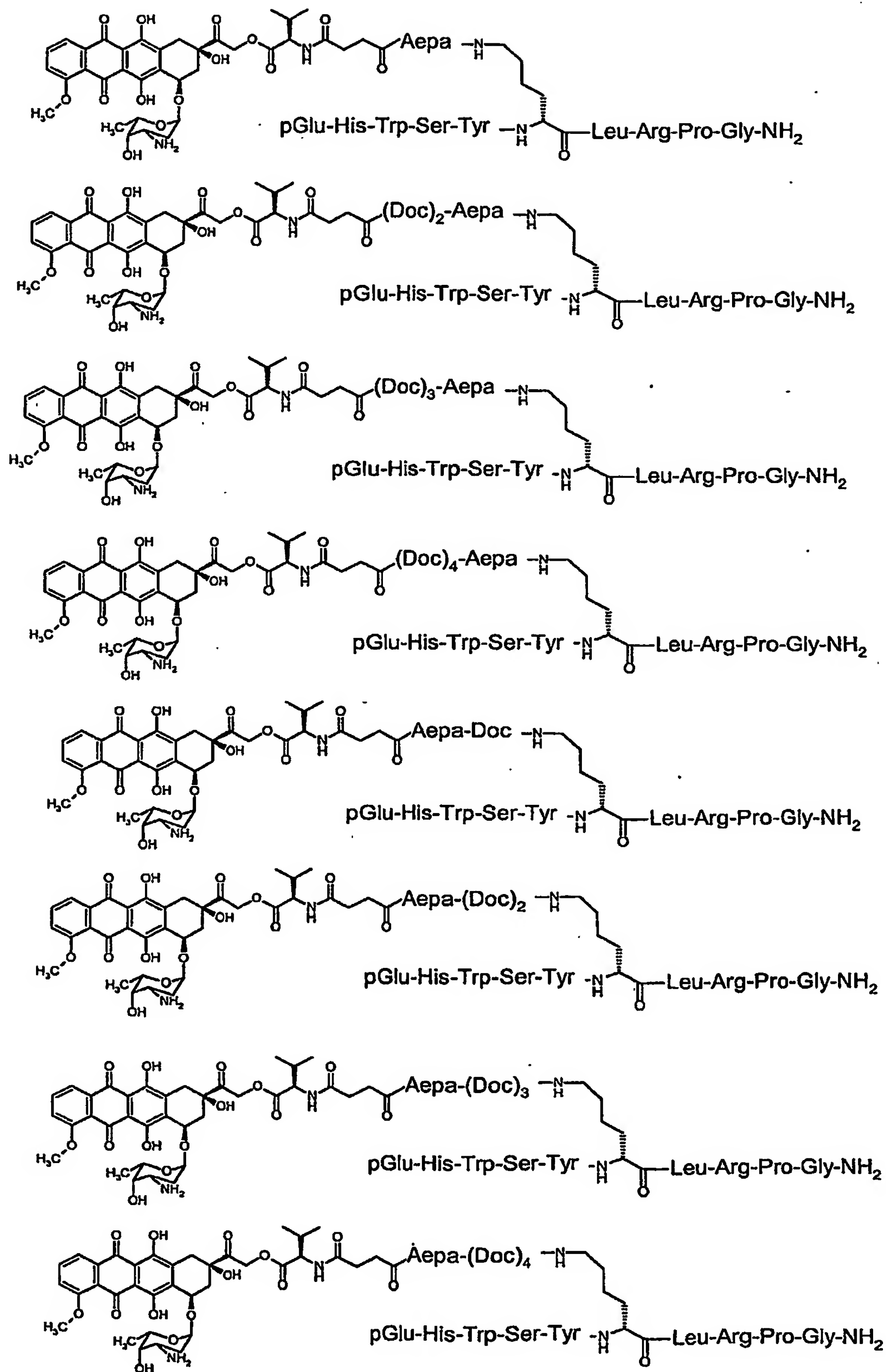


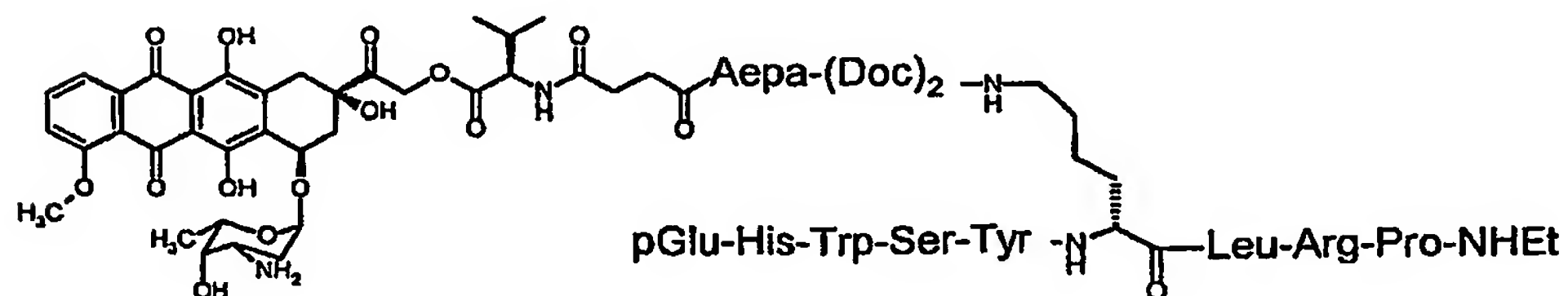
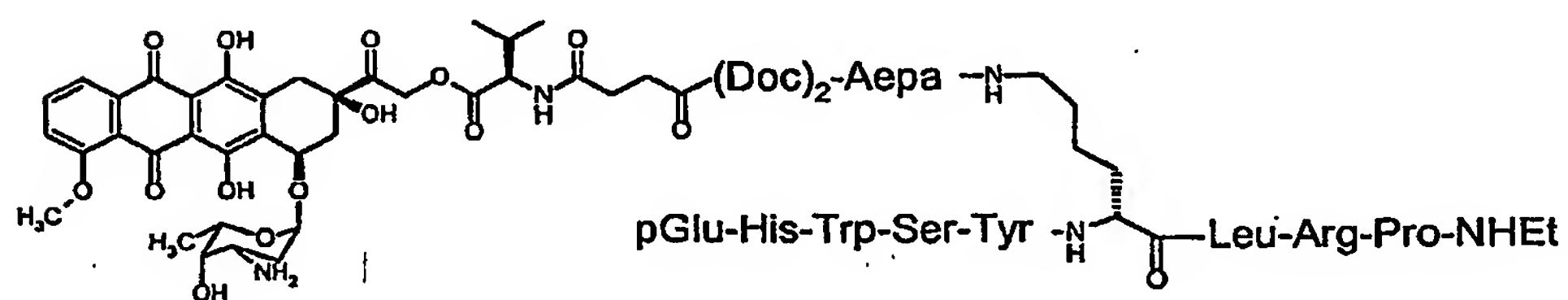
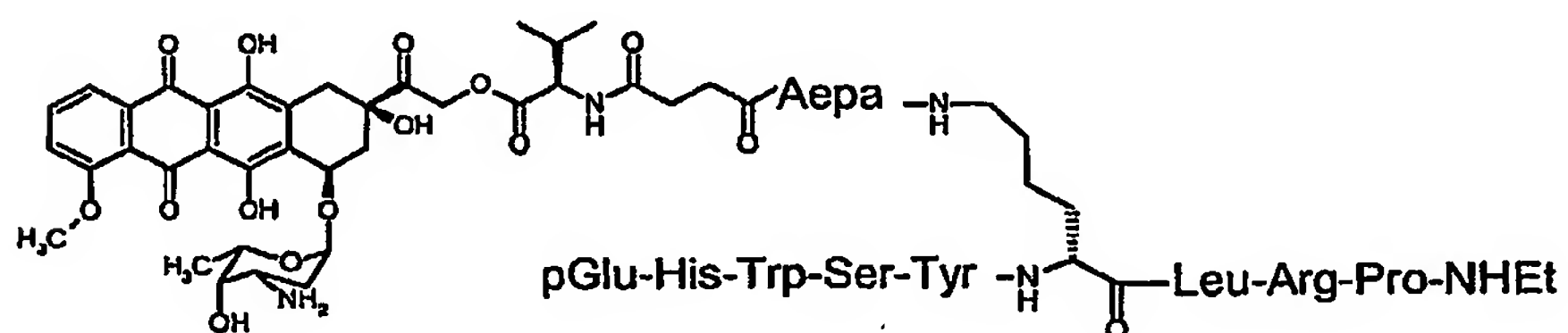
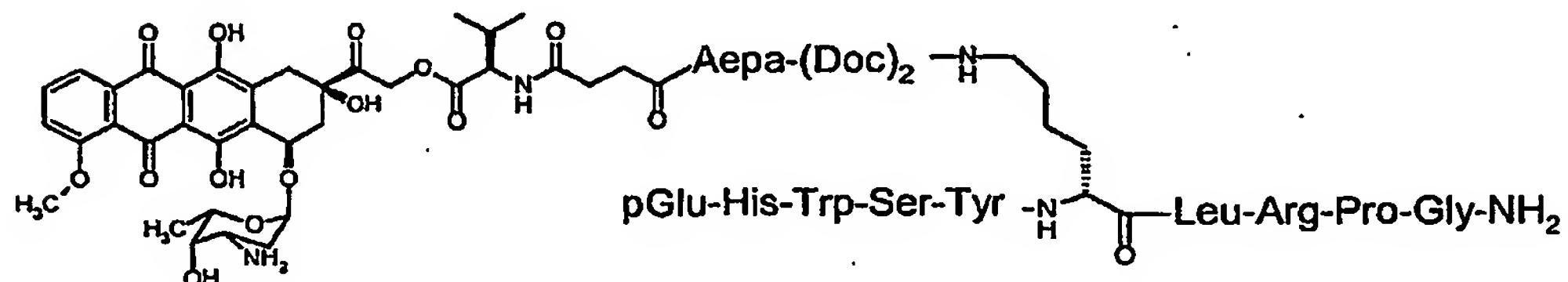
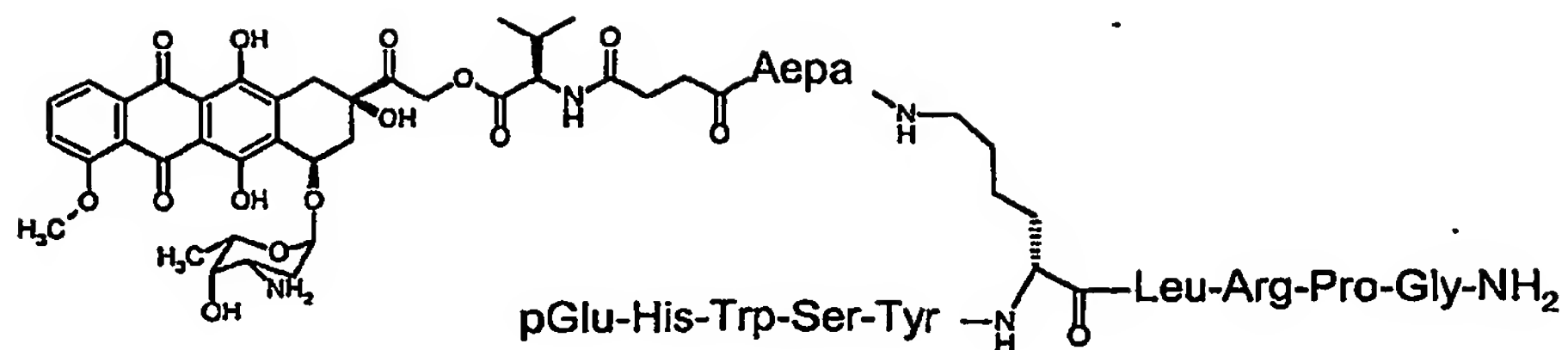


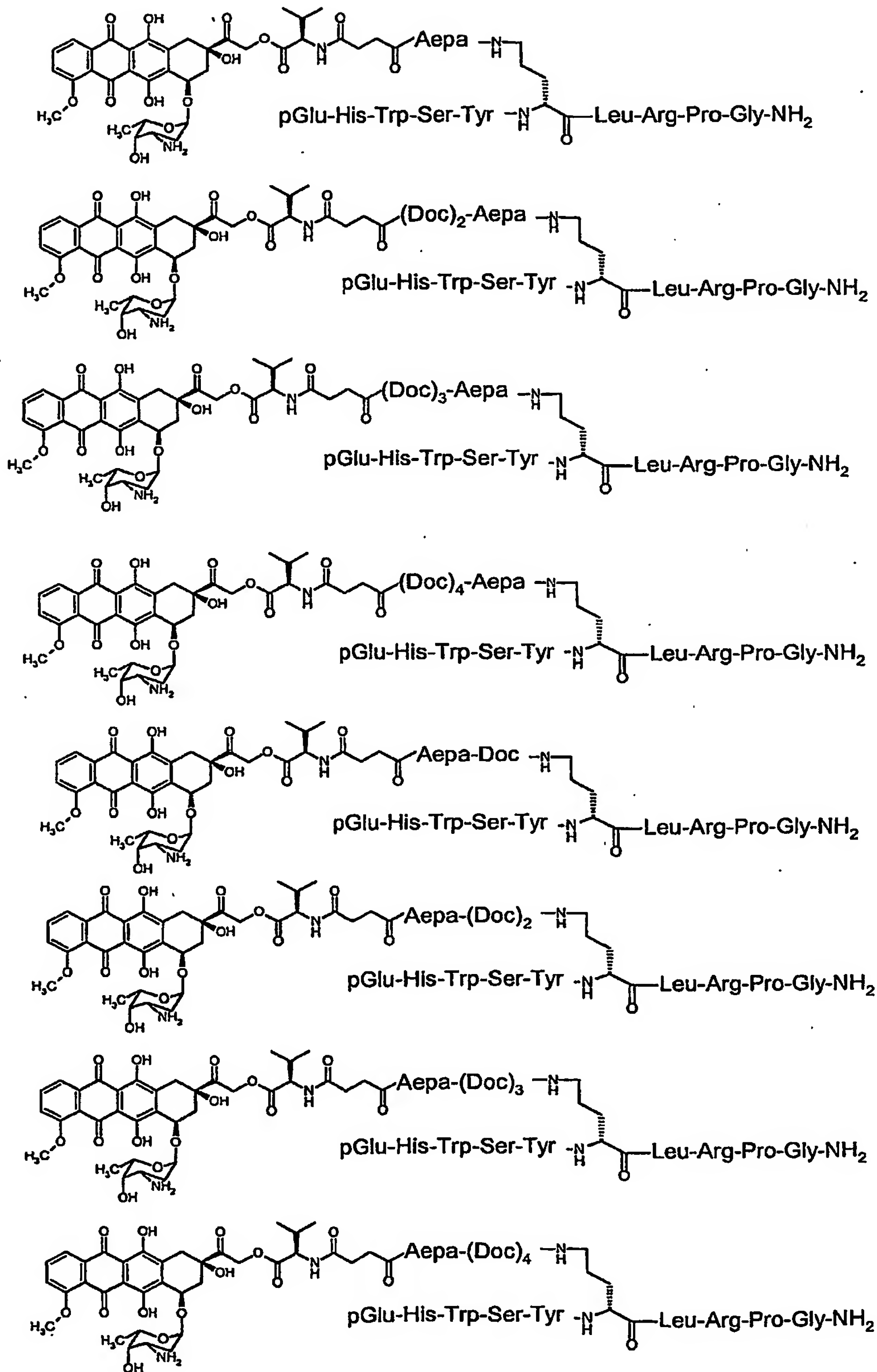


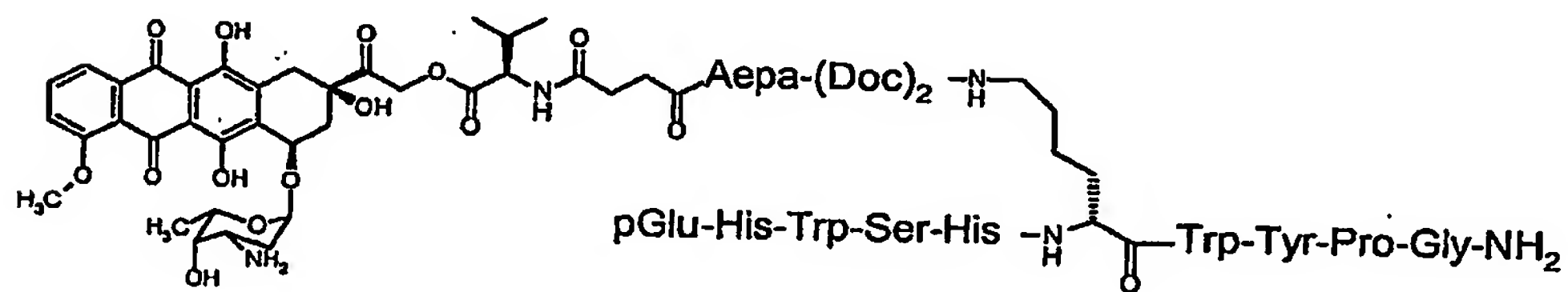
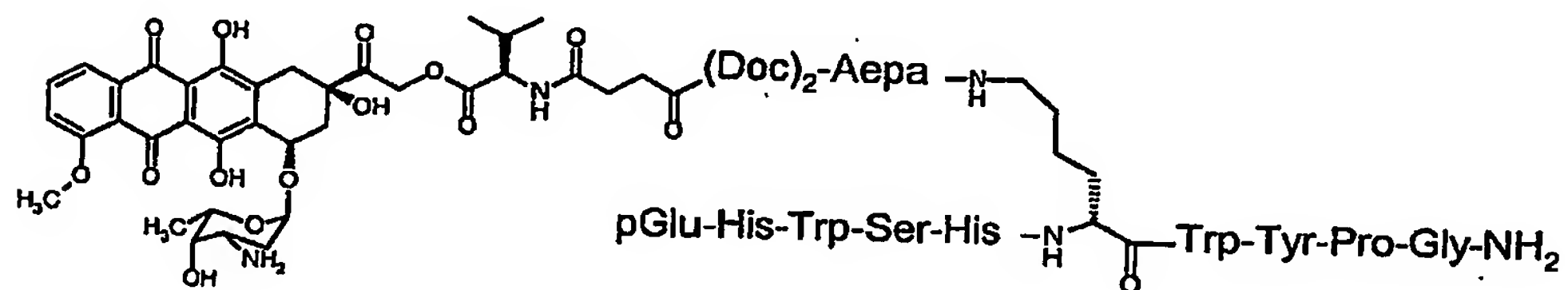
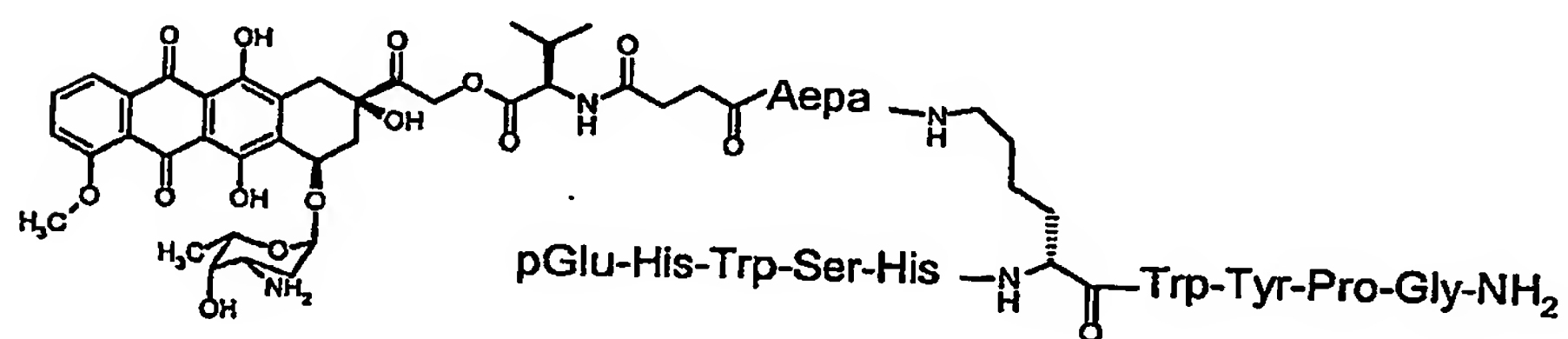
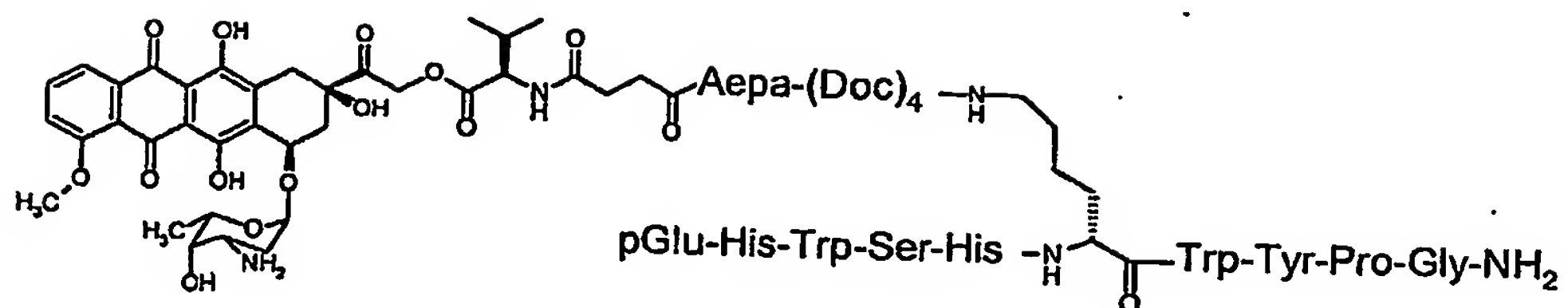




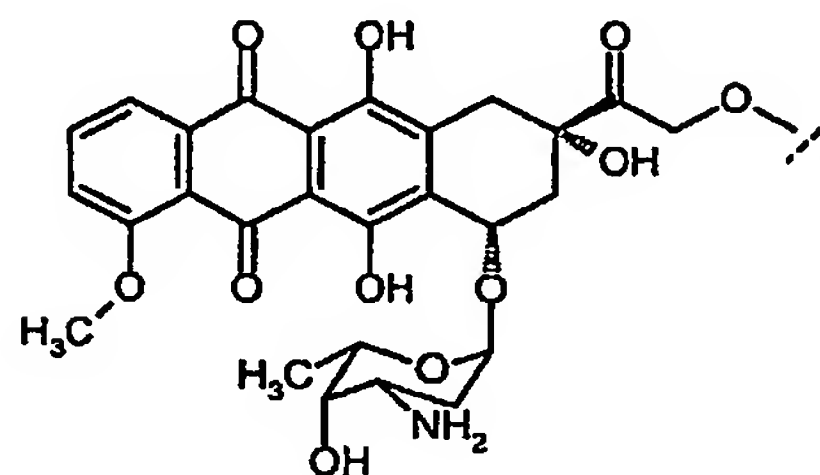
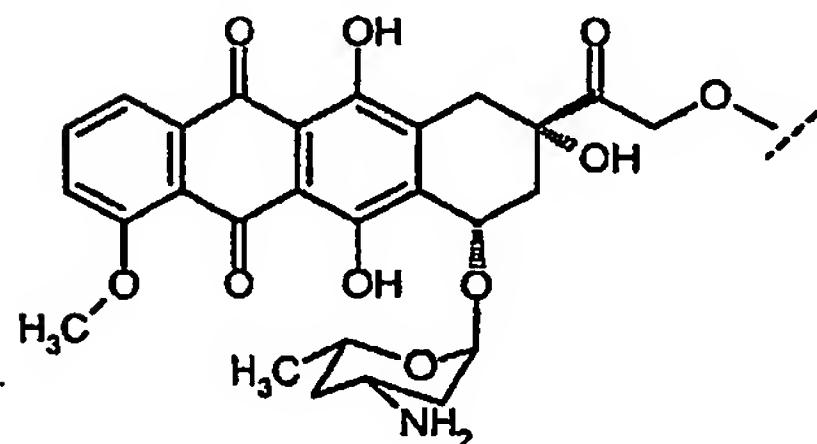
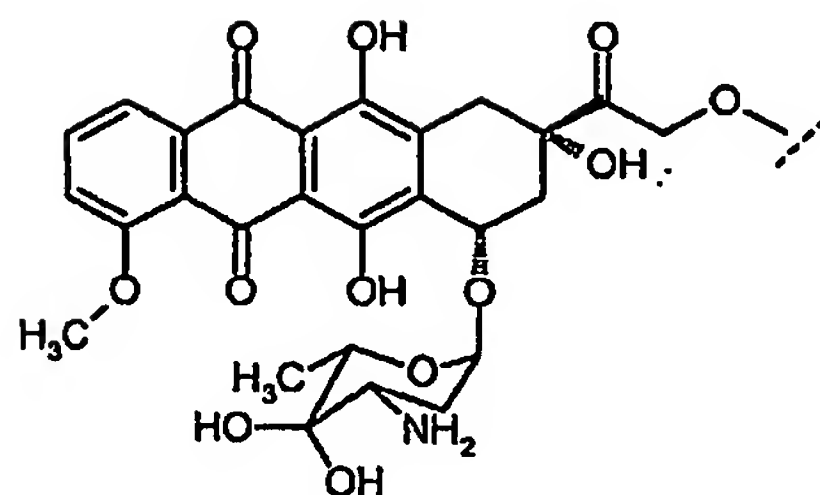
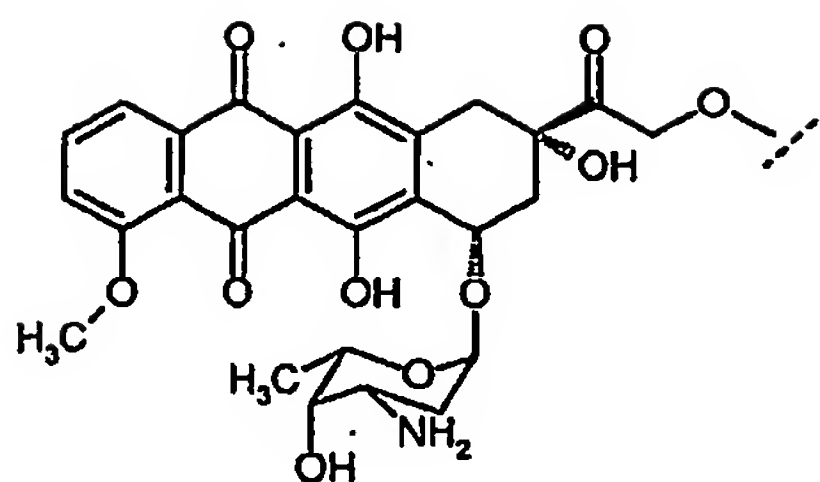


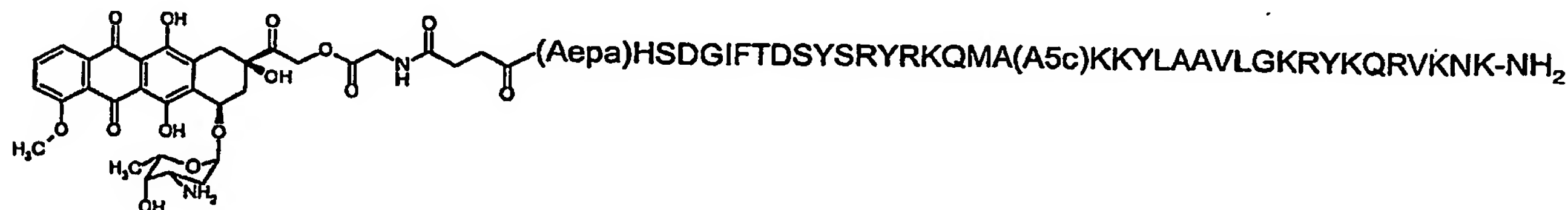
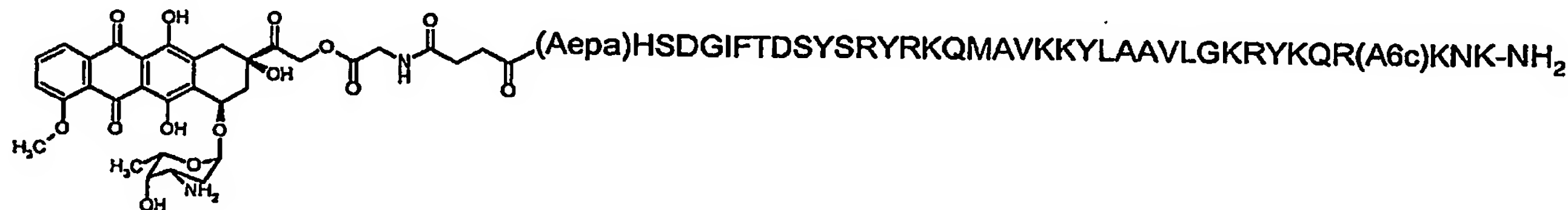
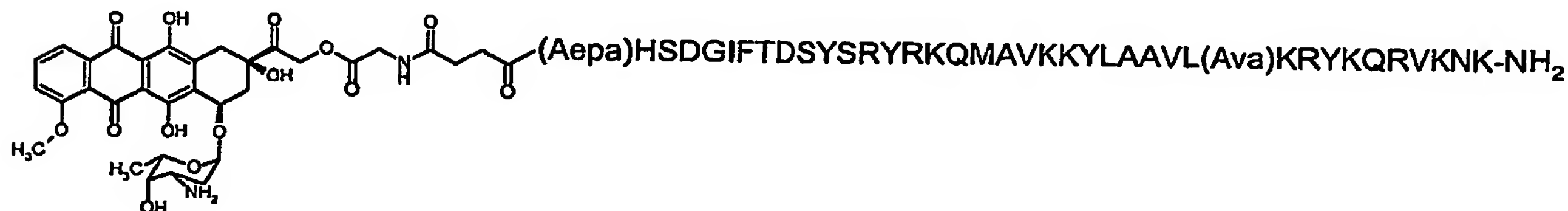
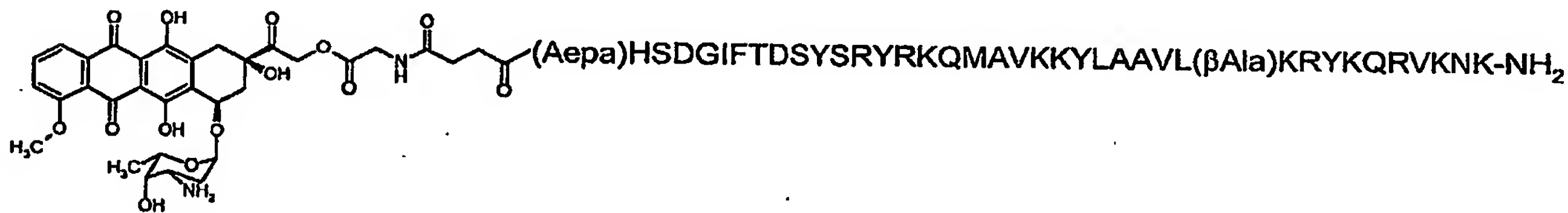
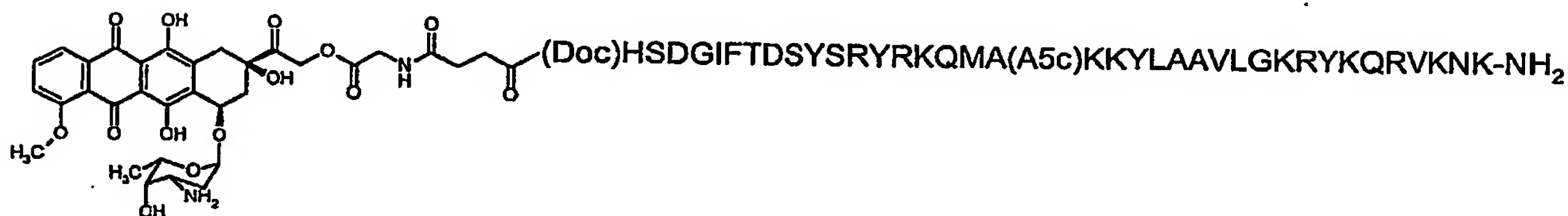
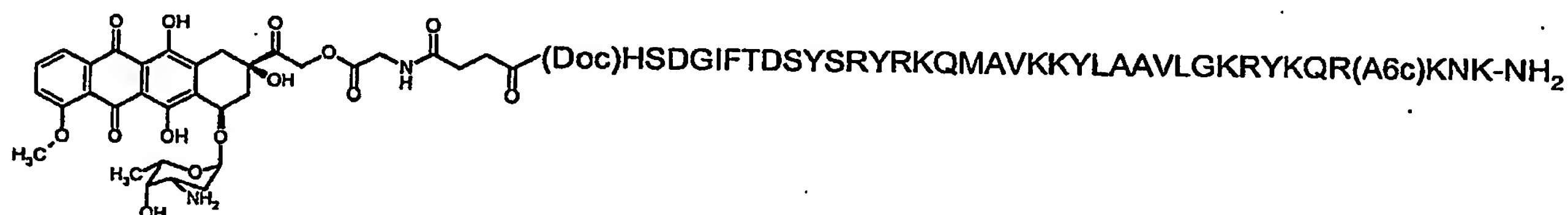
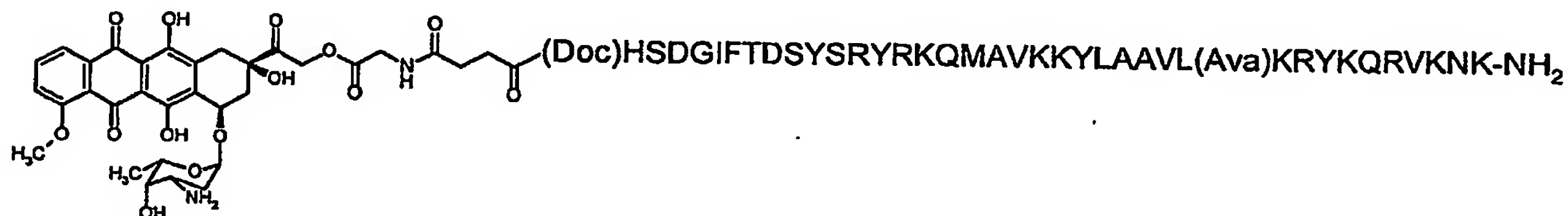
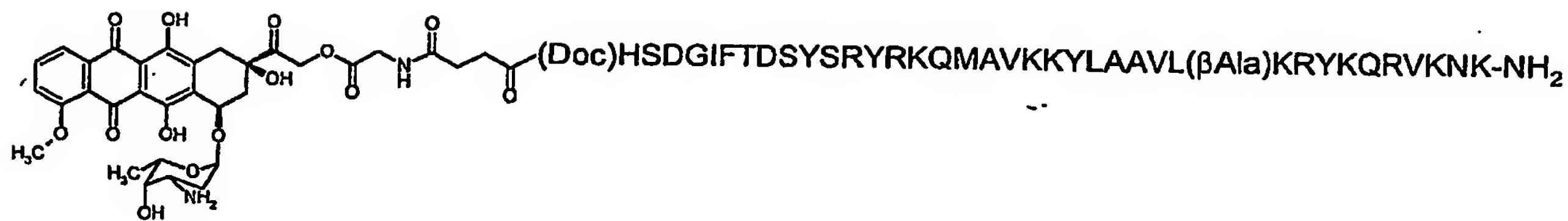


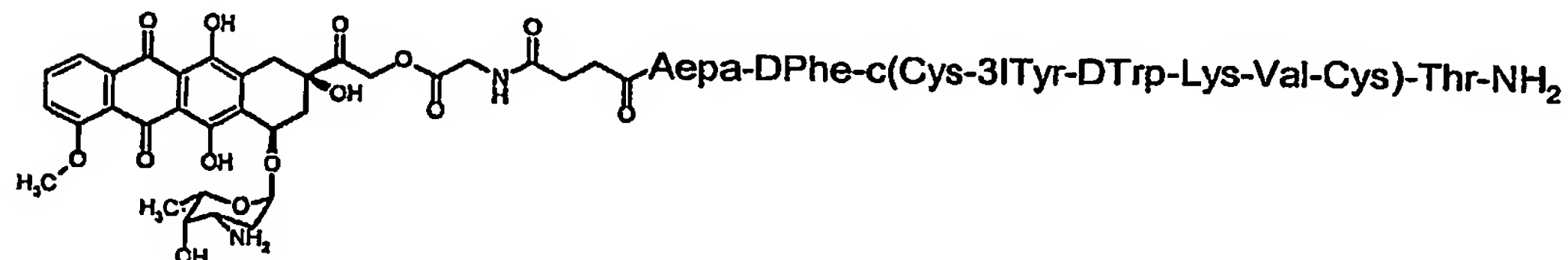
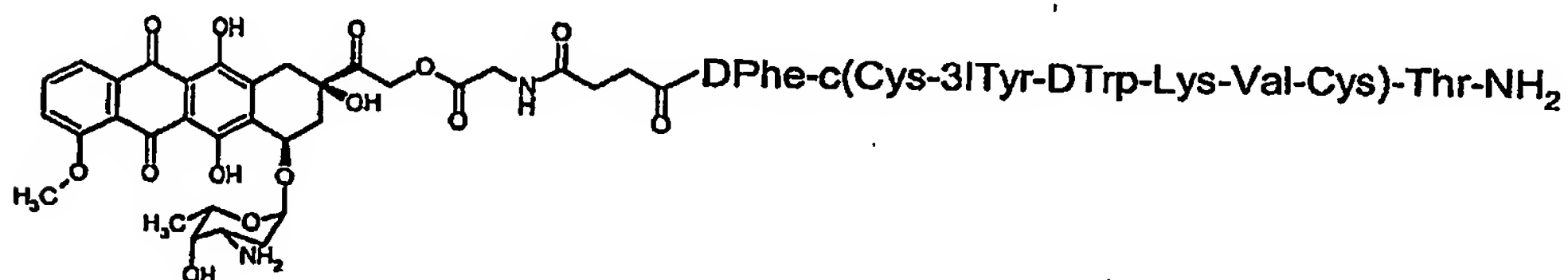
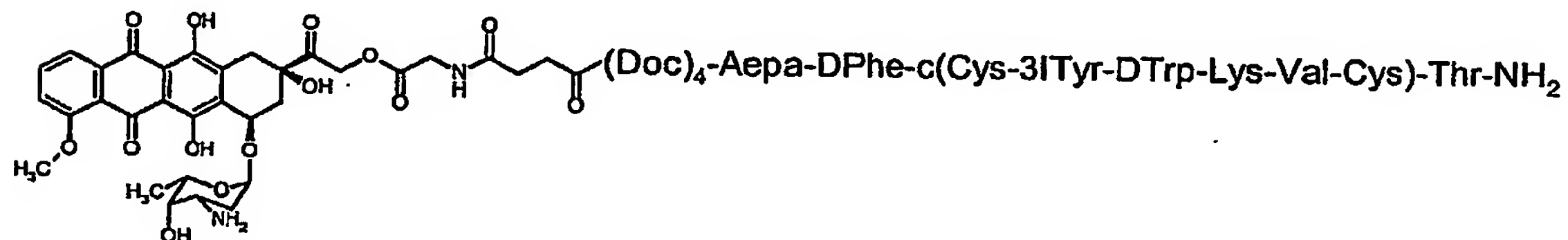
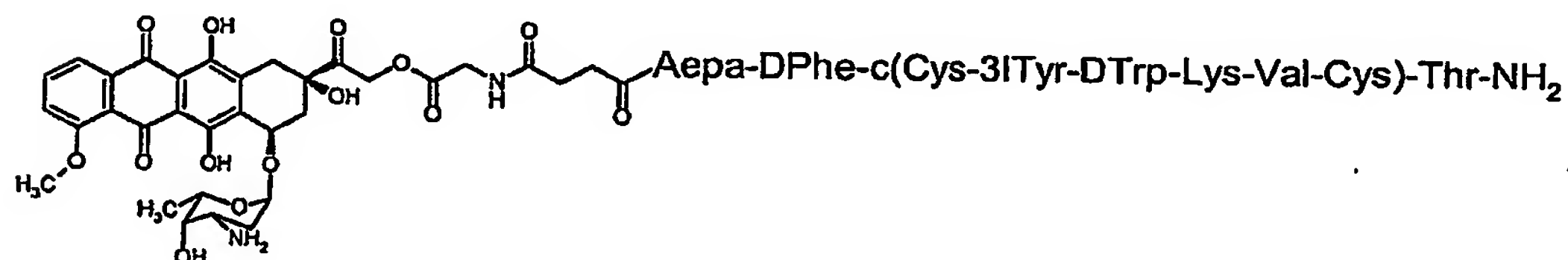
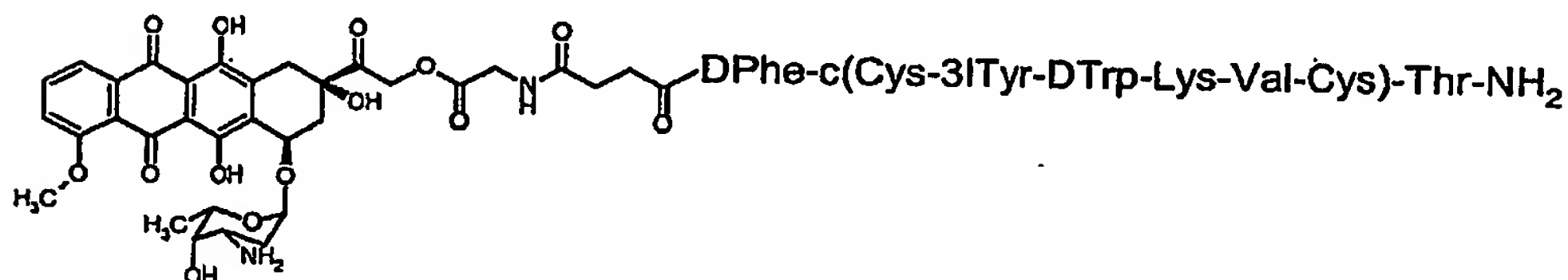
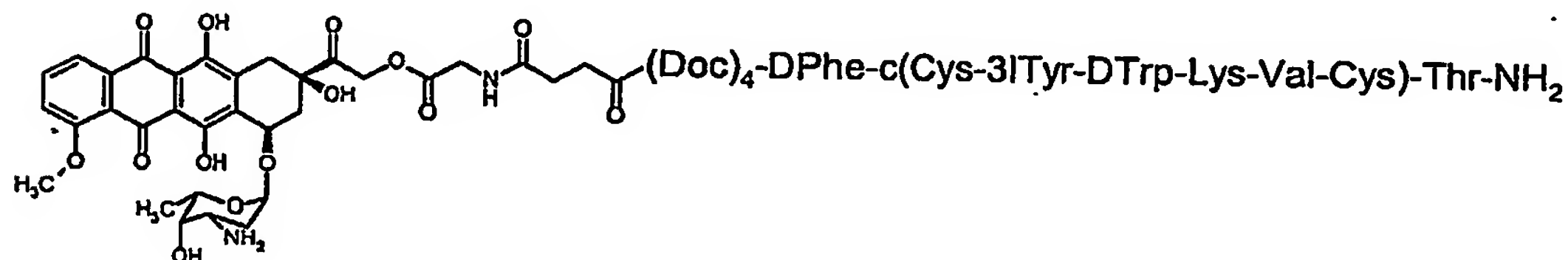
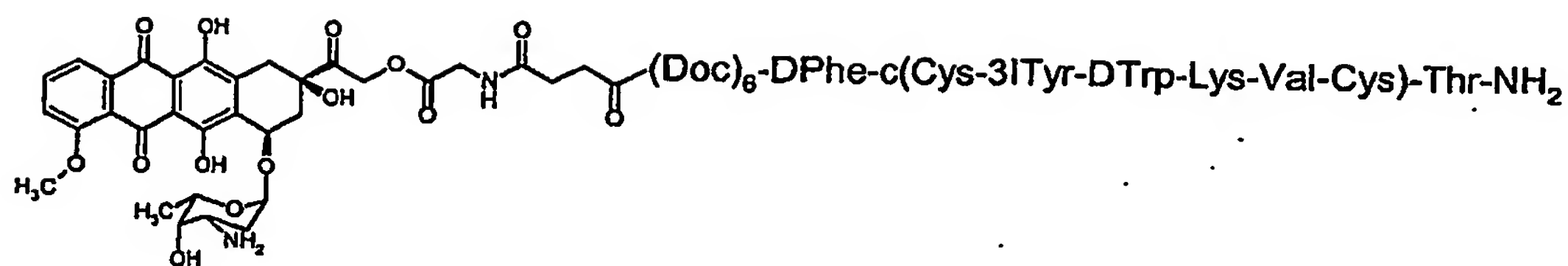


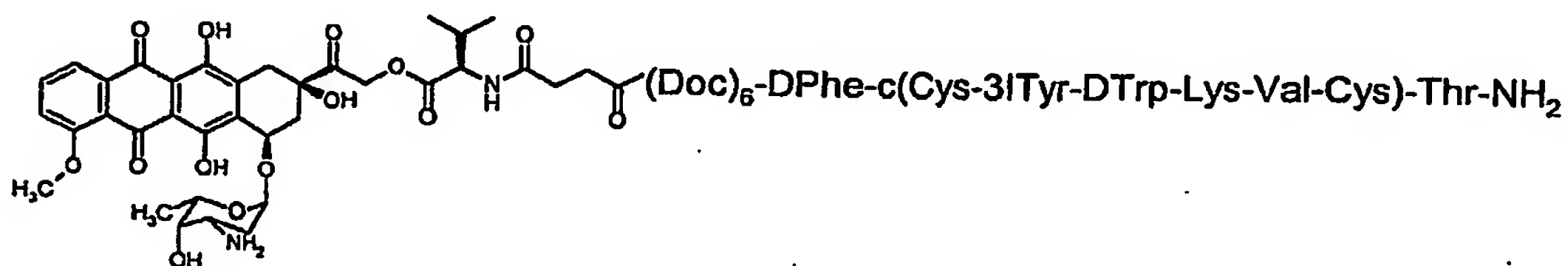
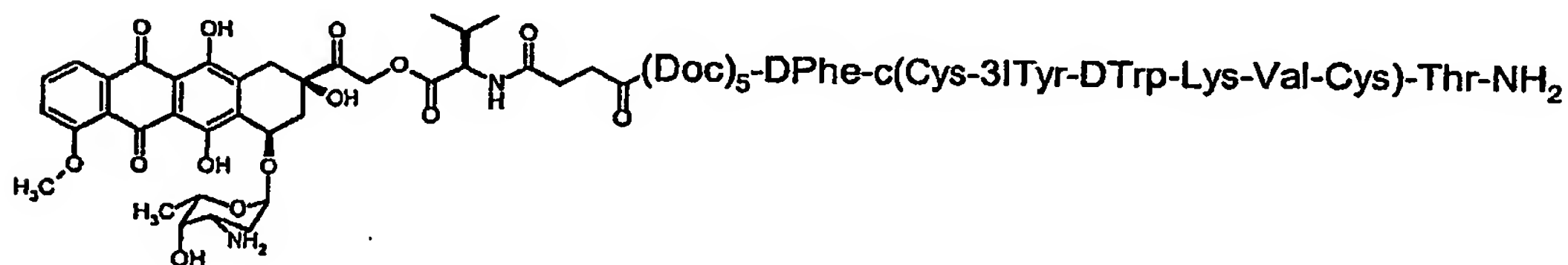
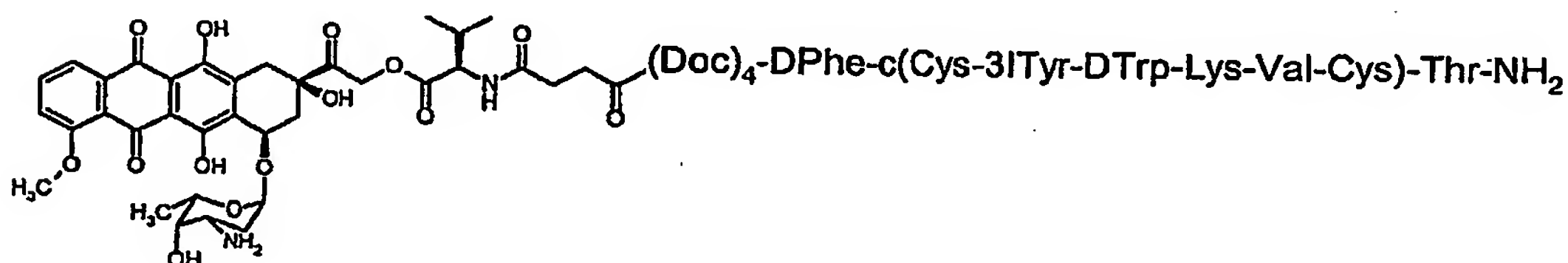
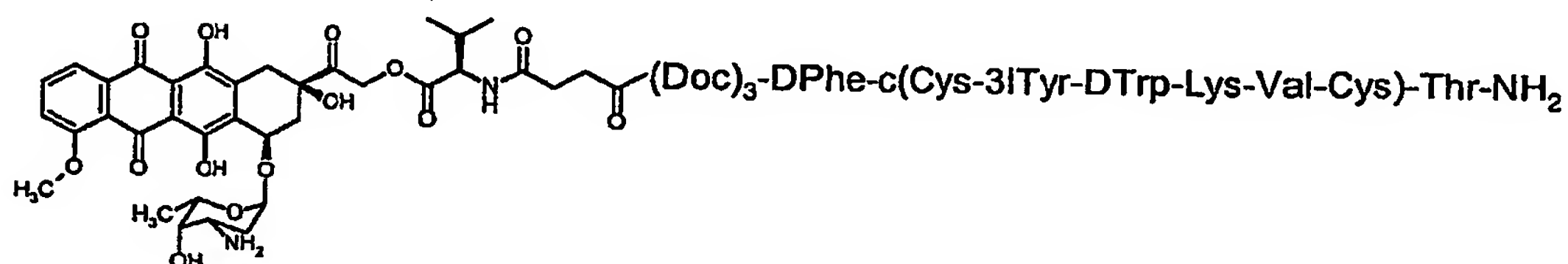
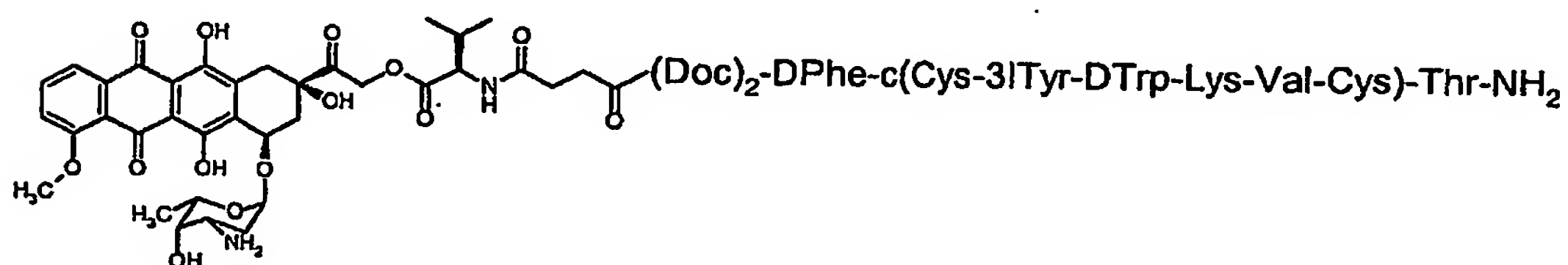
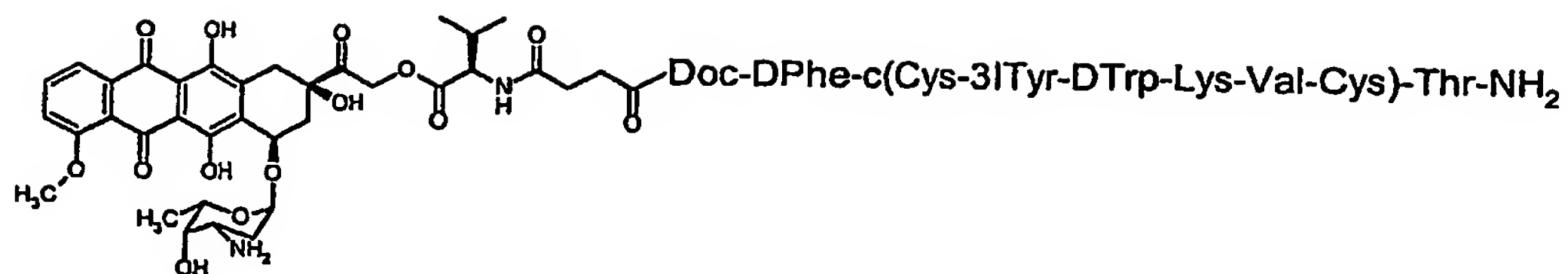


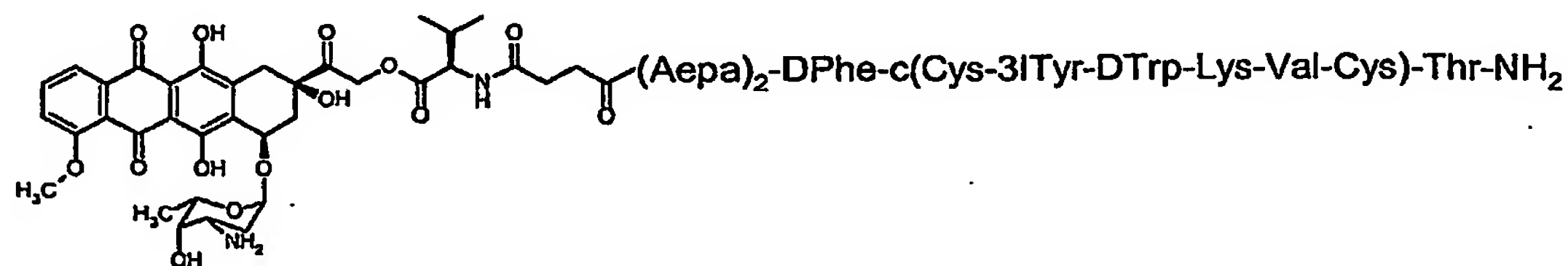
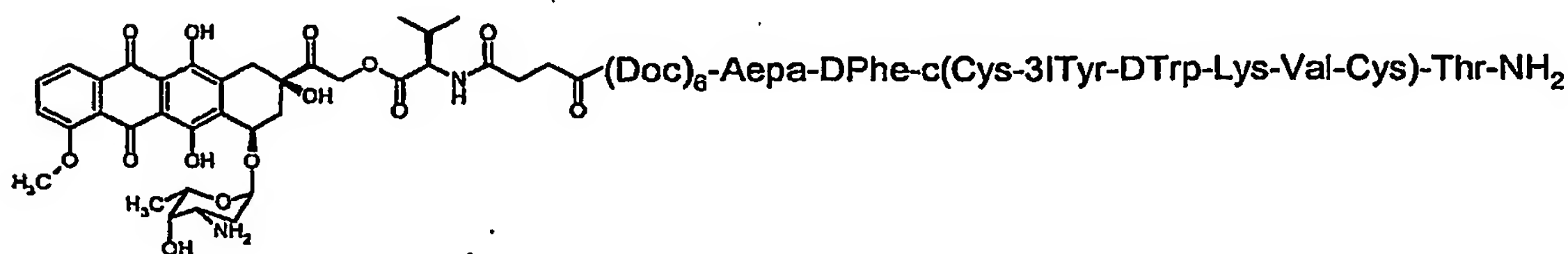
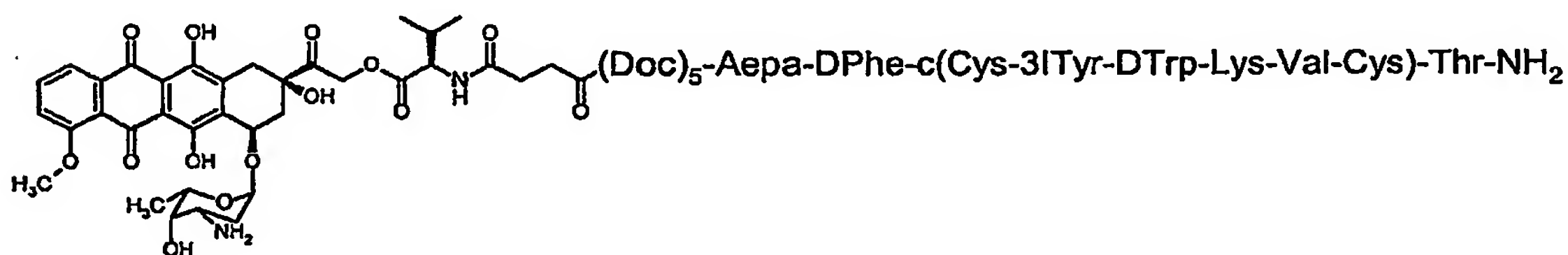
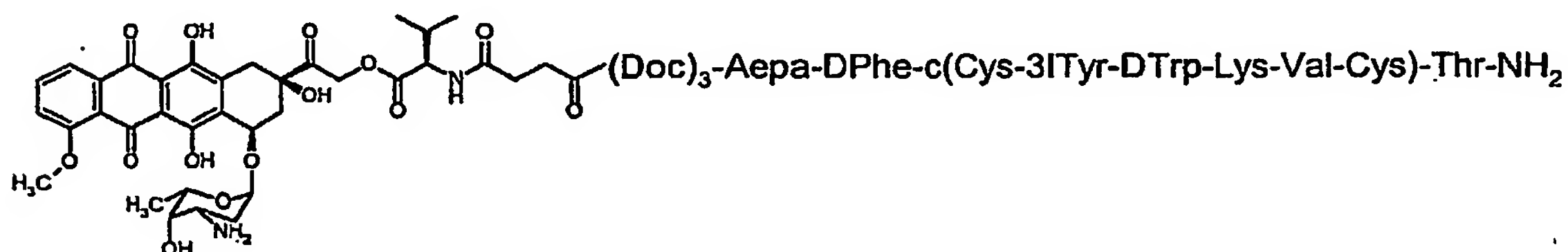
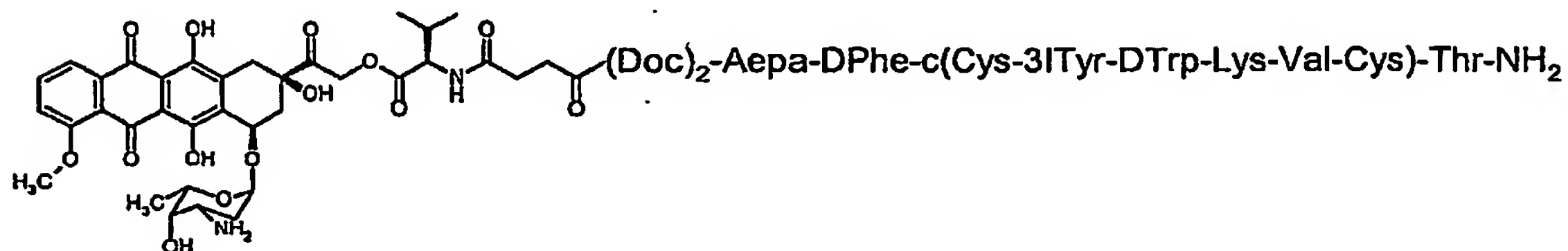
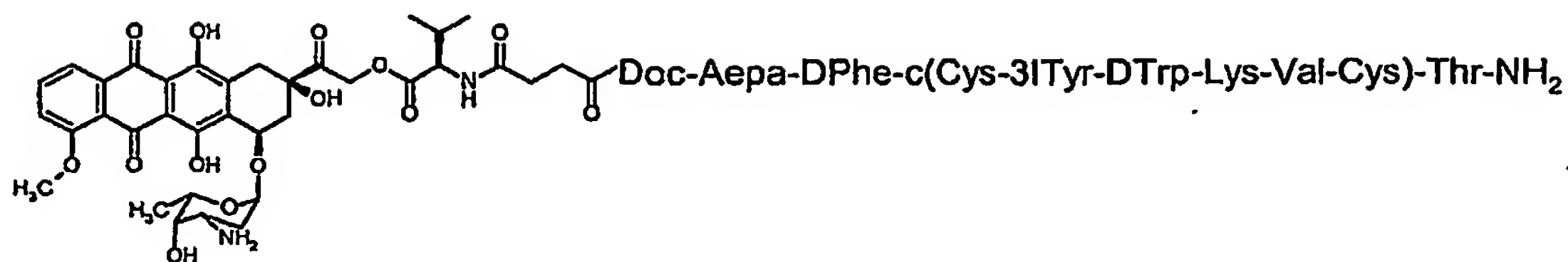
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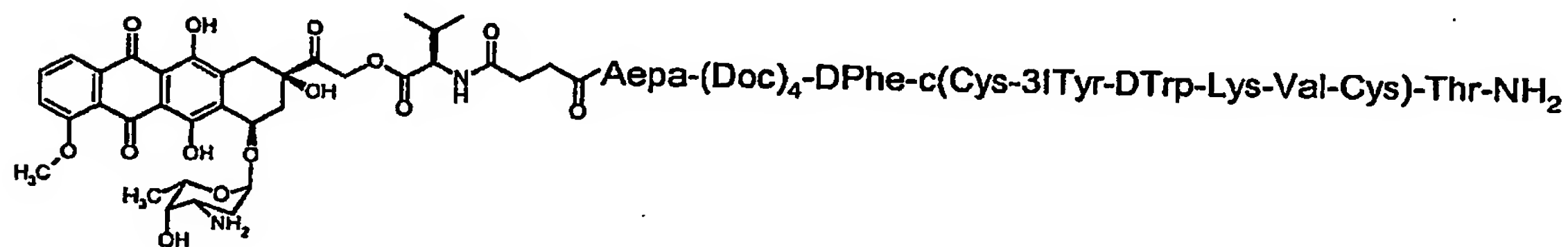
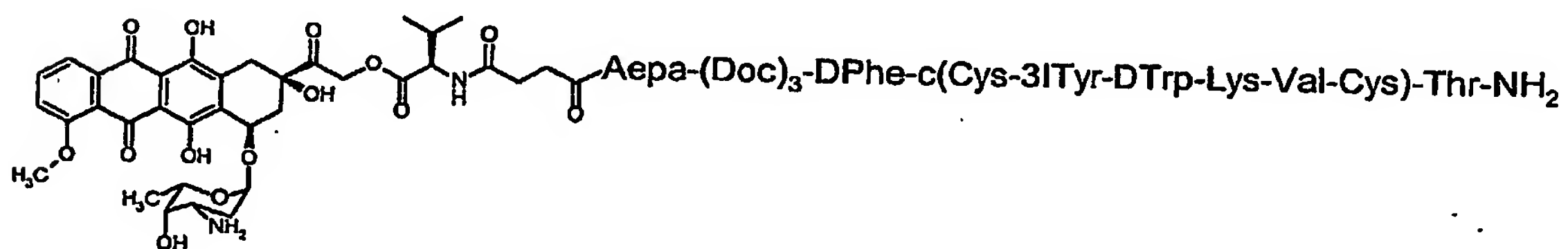
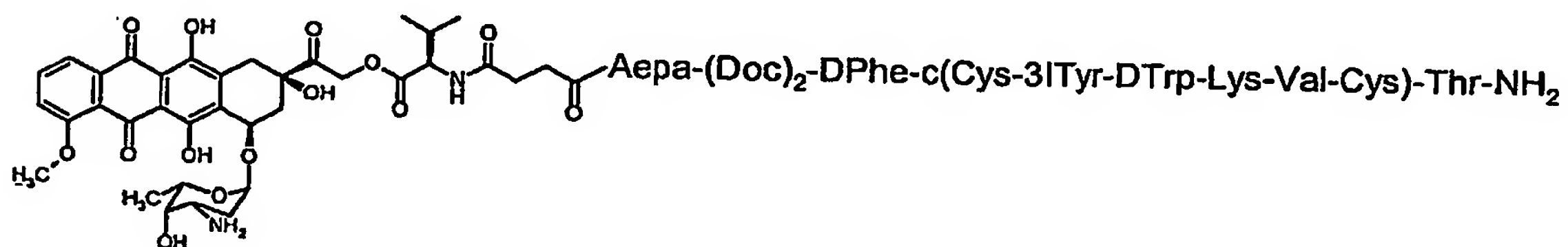
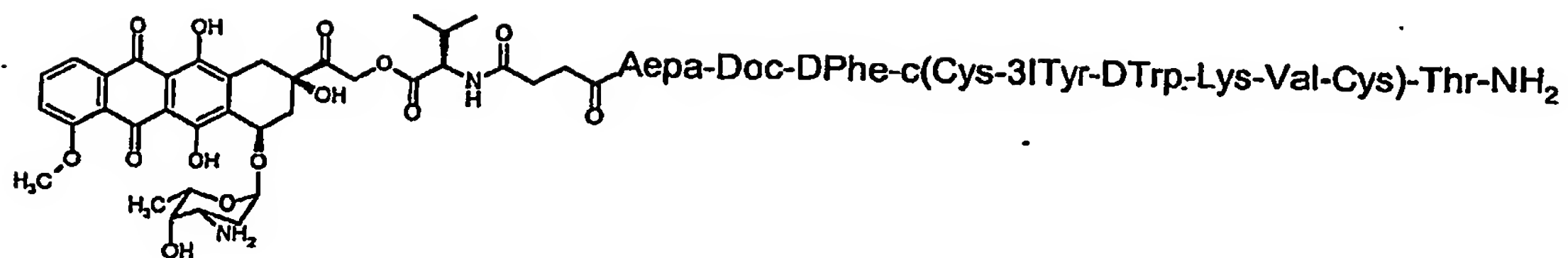




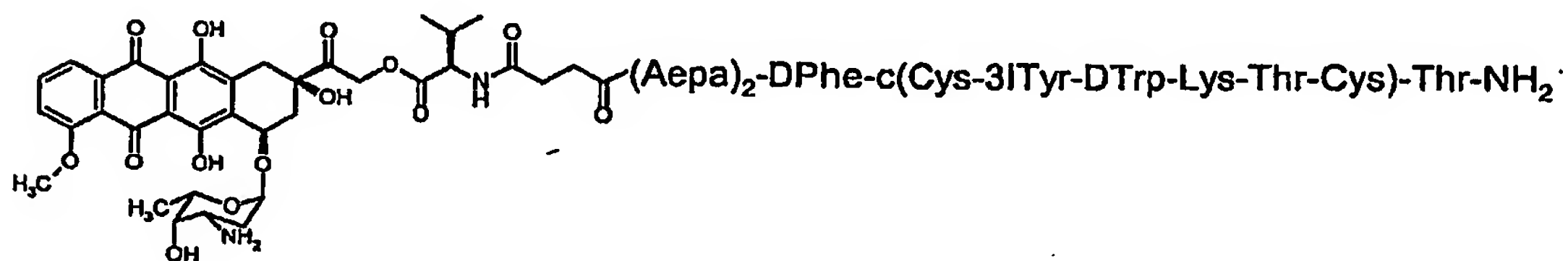
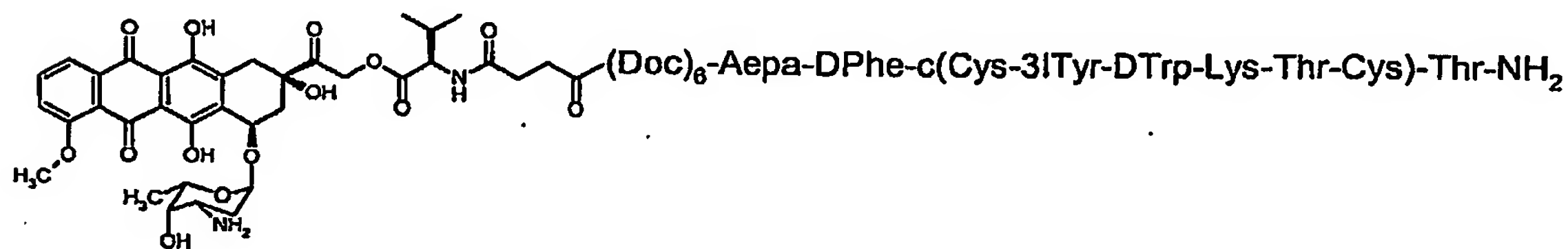
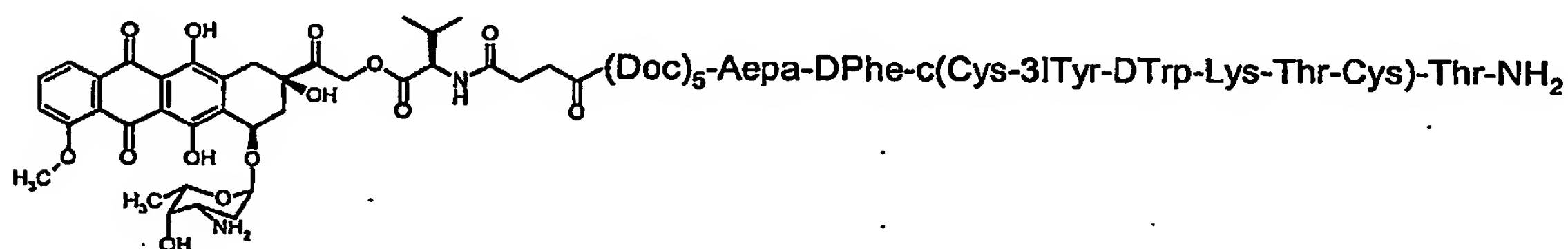
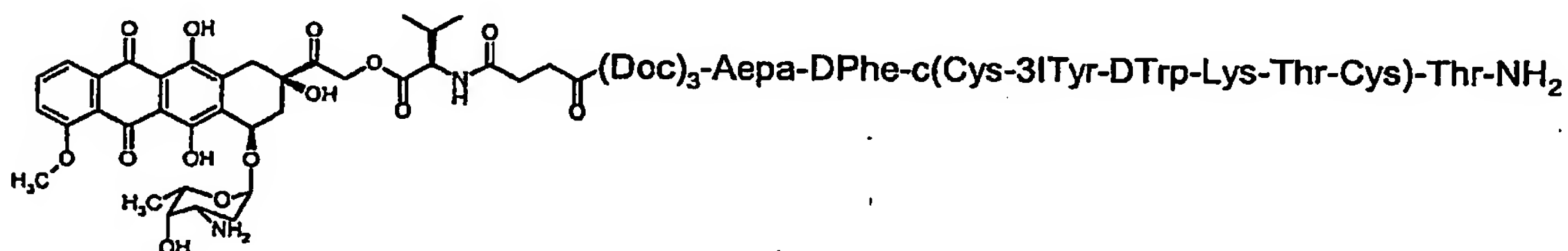
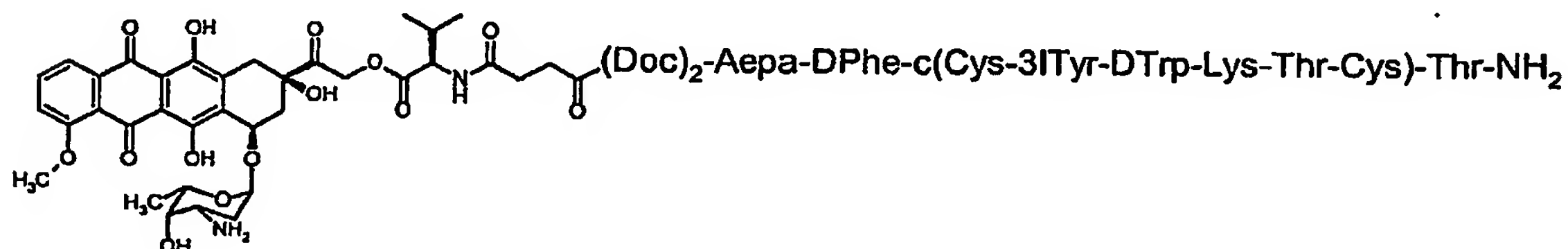
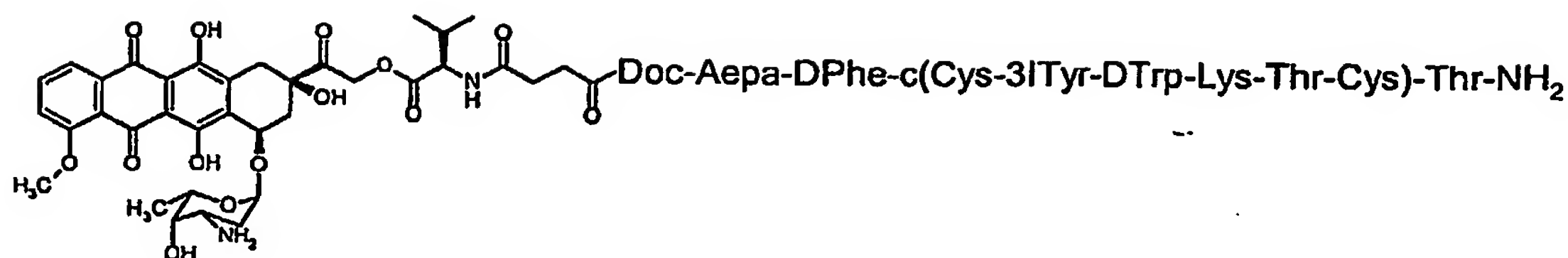
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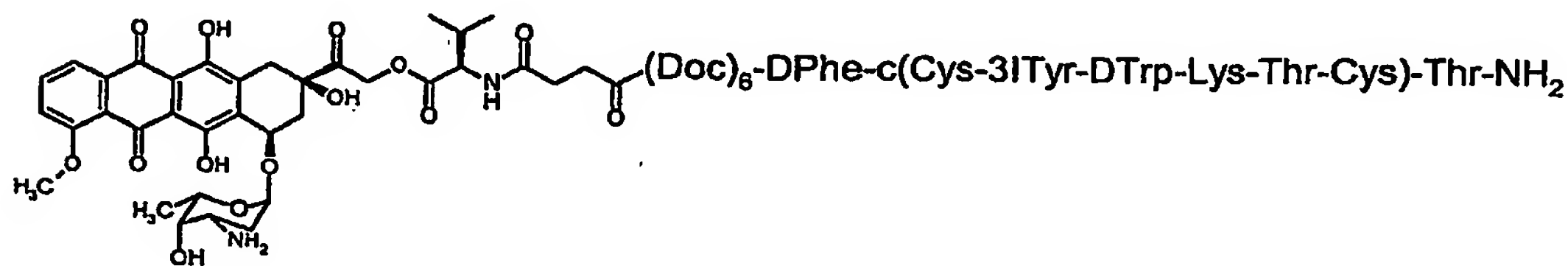
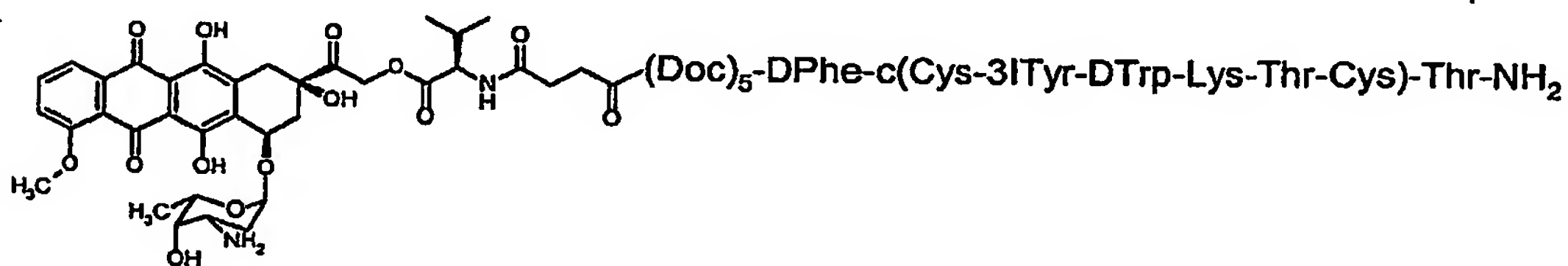
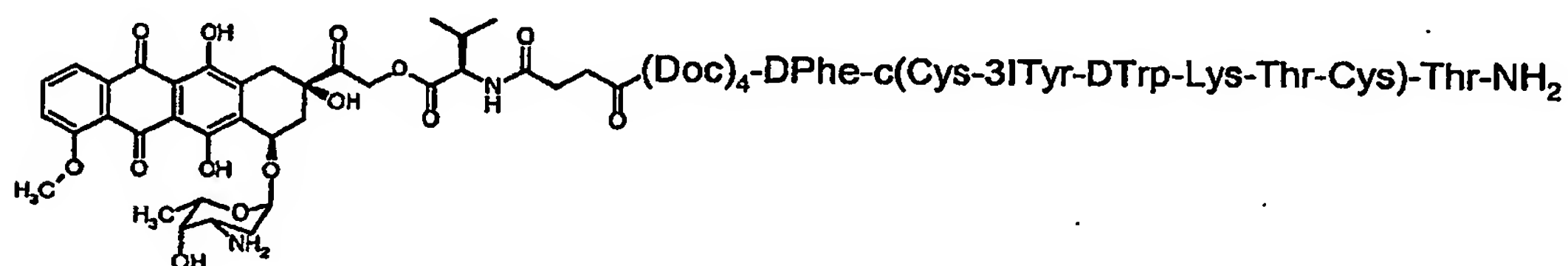
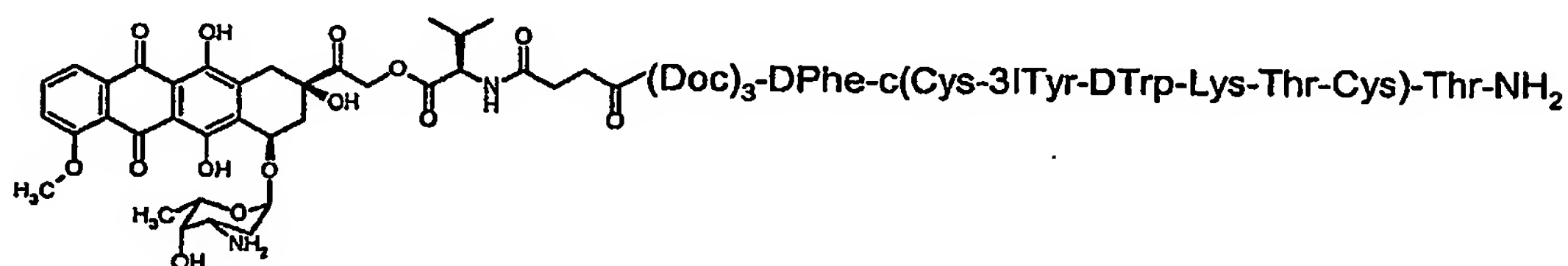
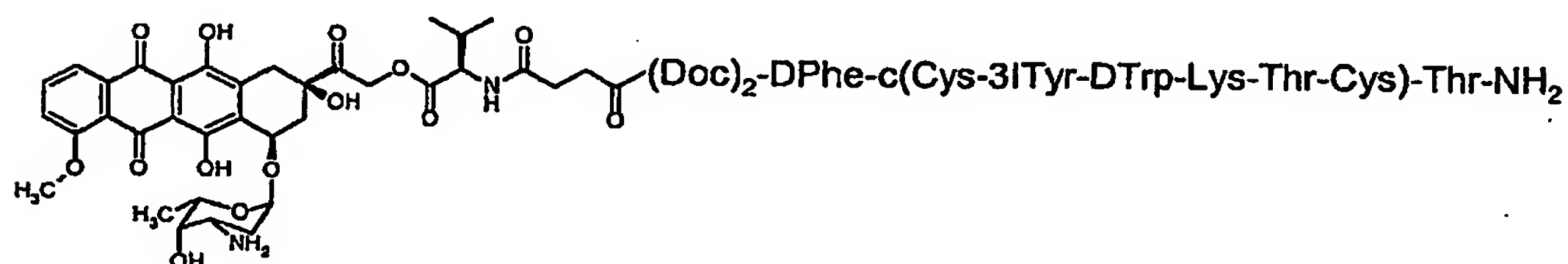
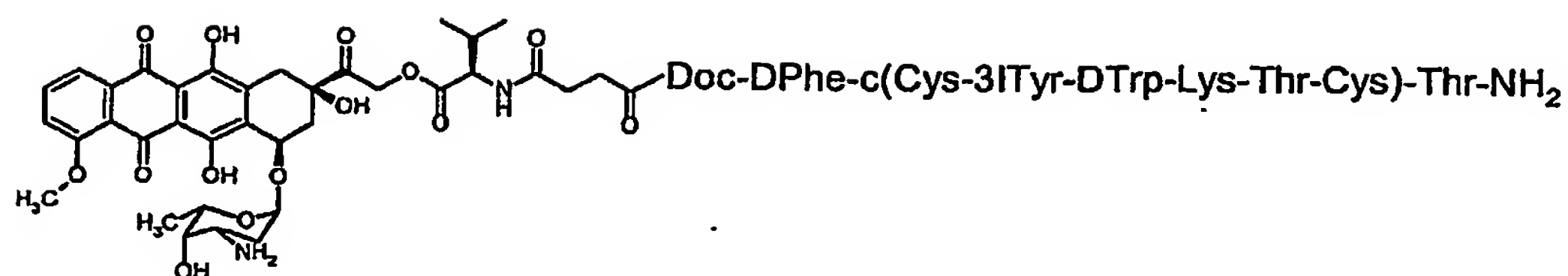
Appendix G

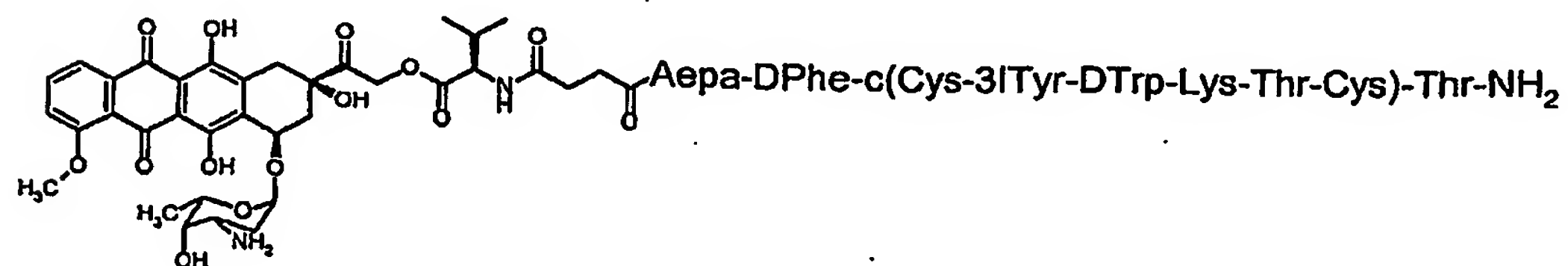
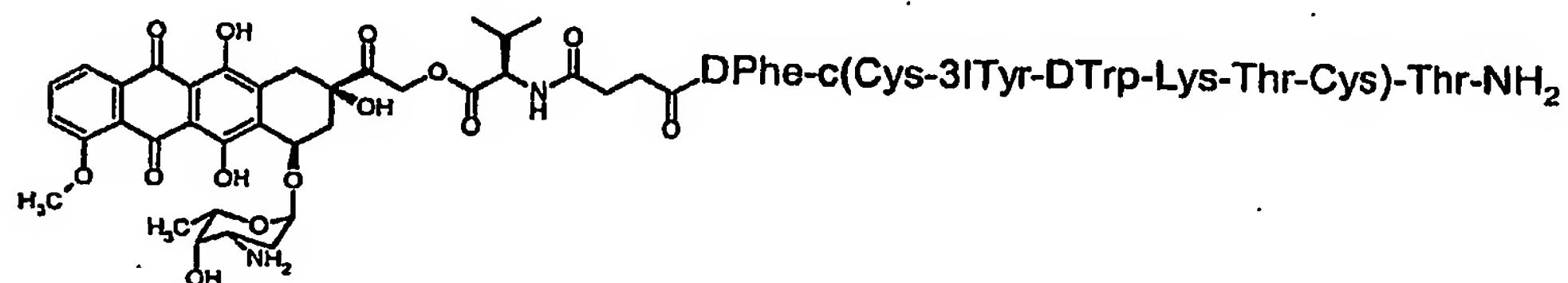
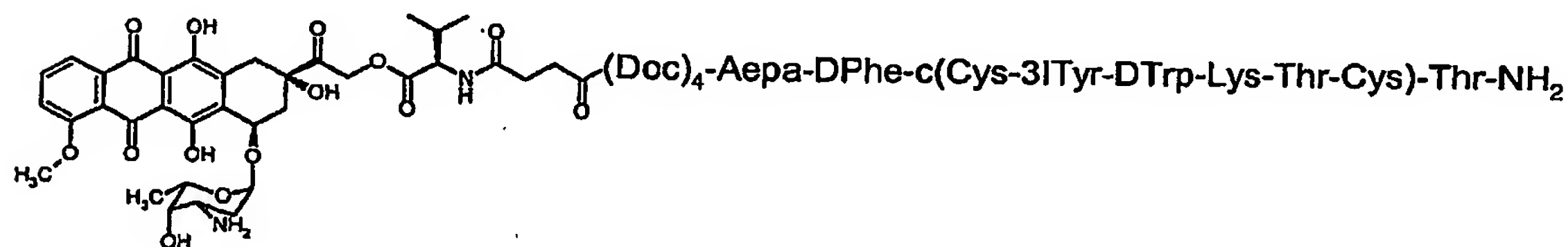
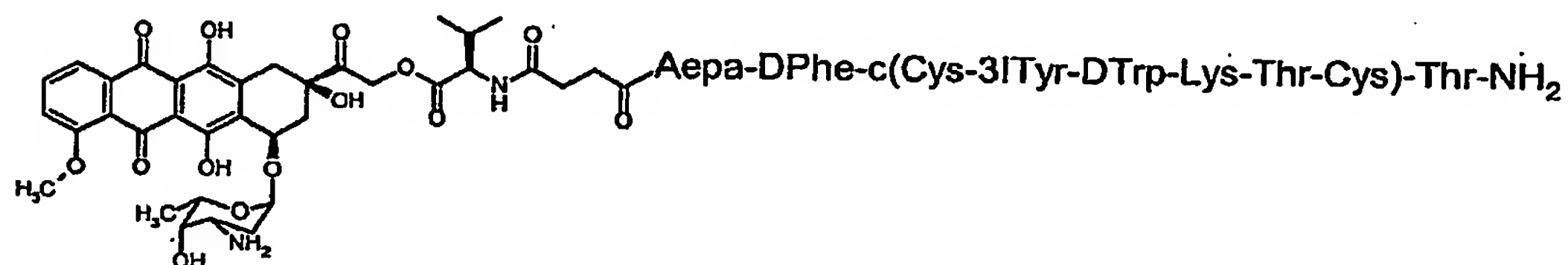
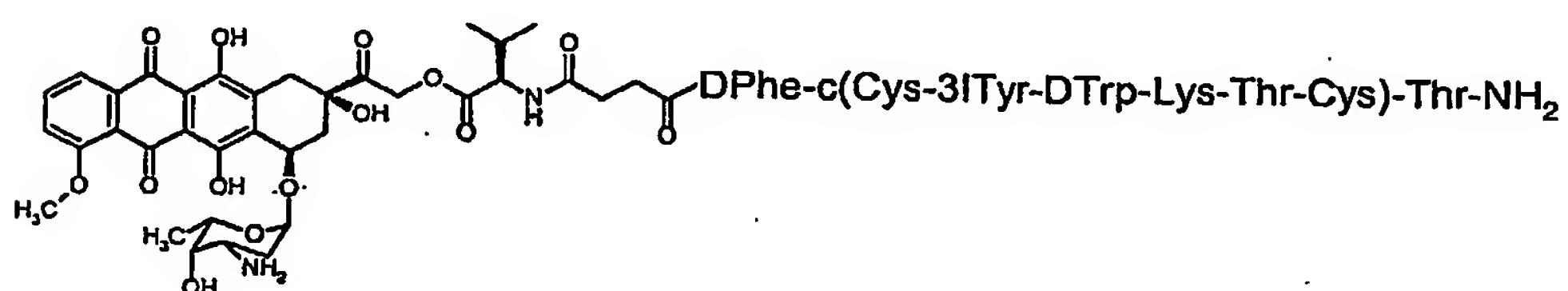
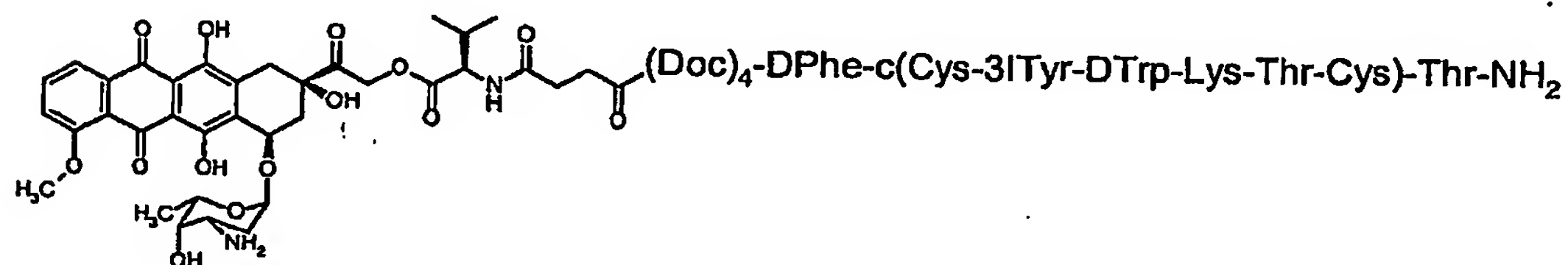
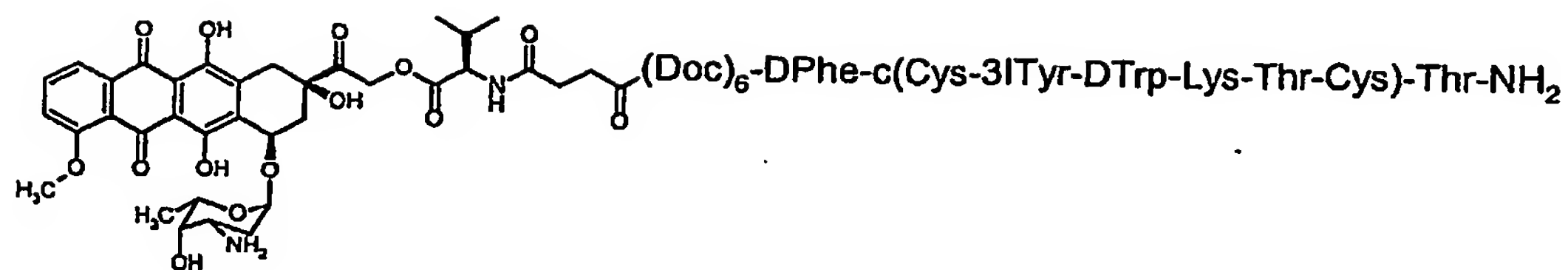
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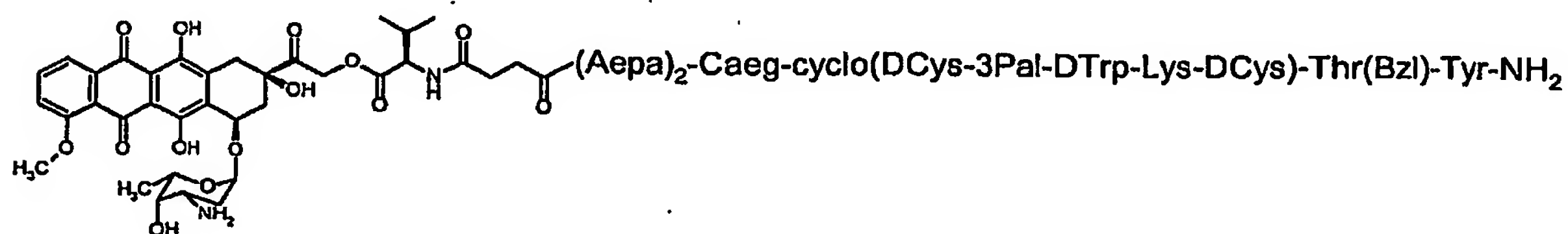
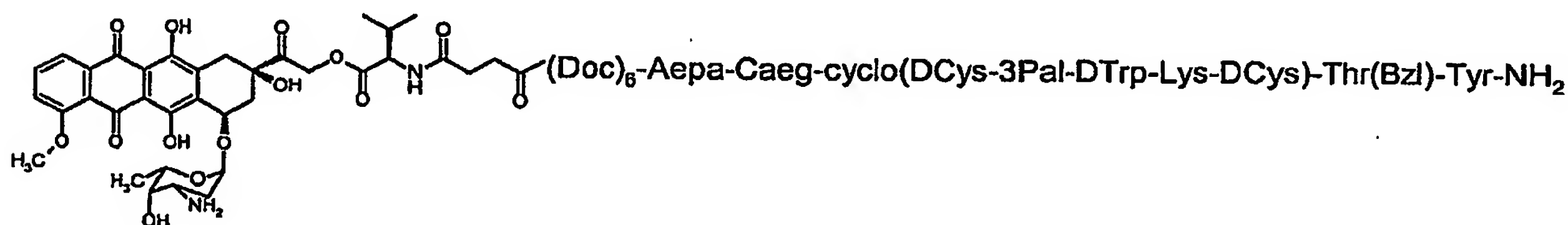
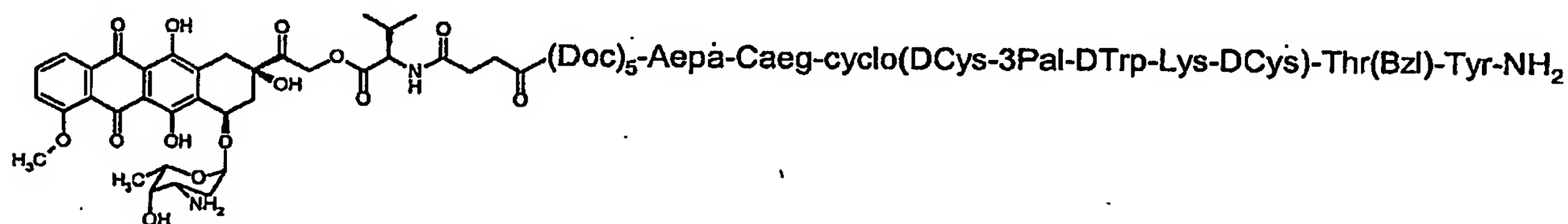
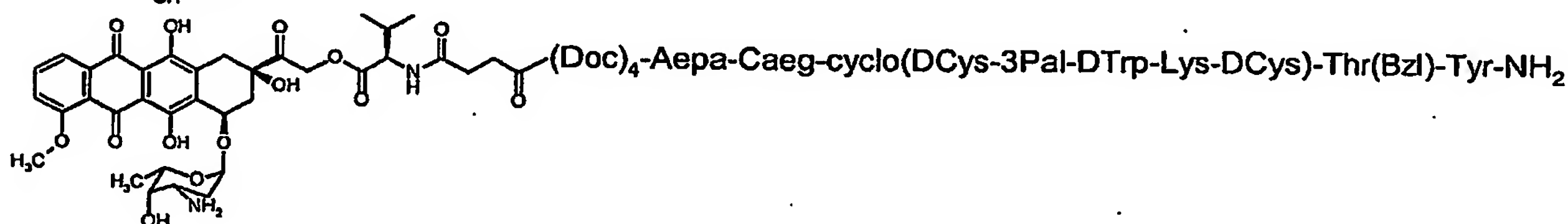
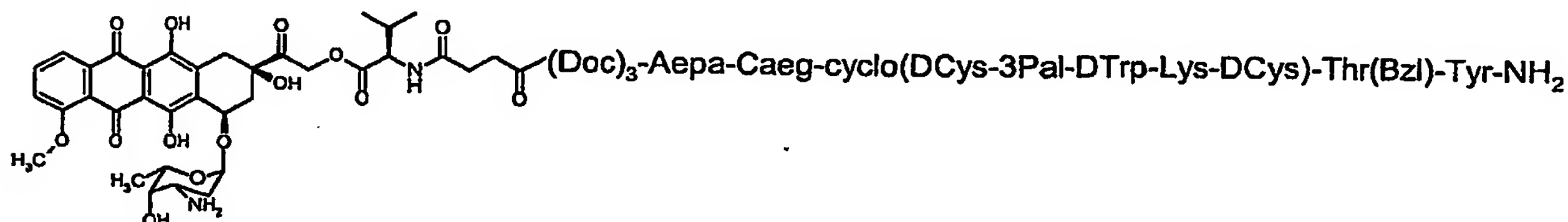
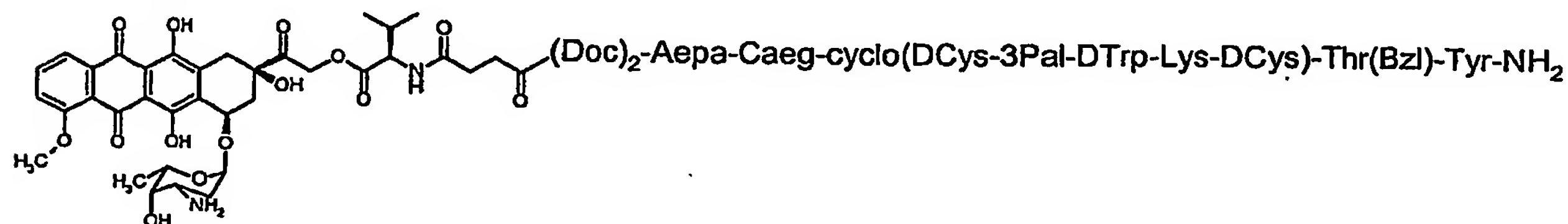
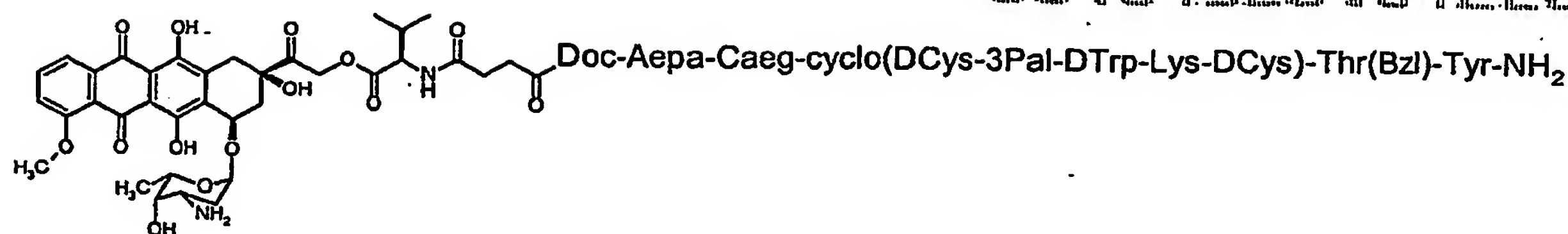


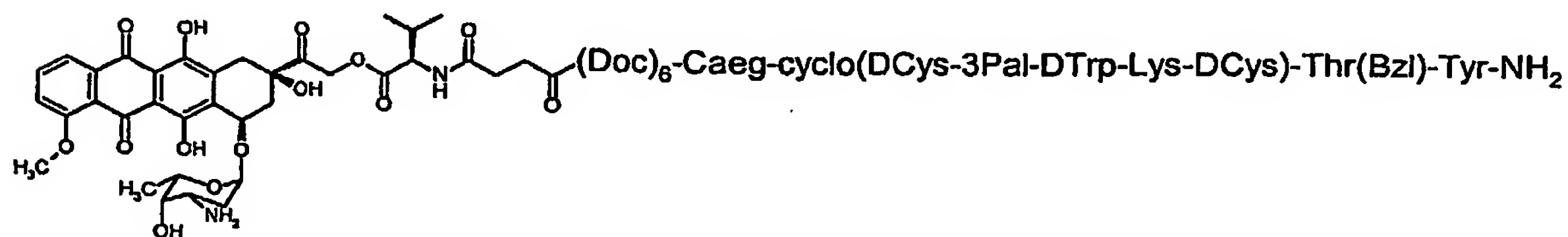
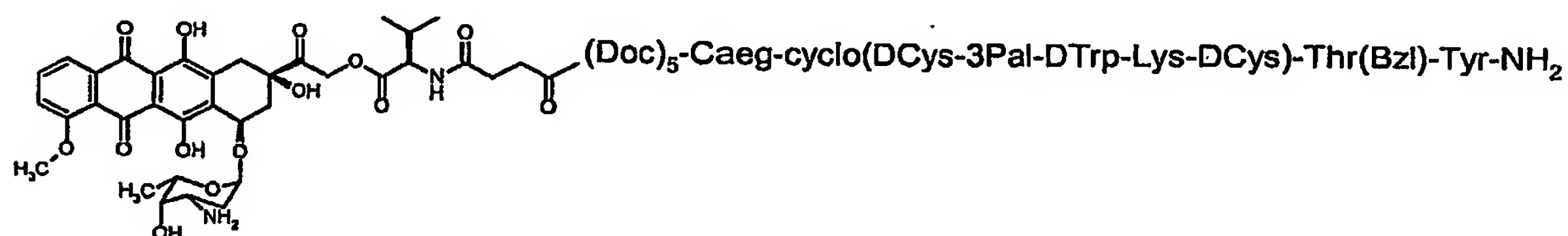
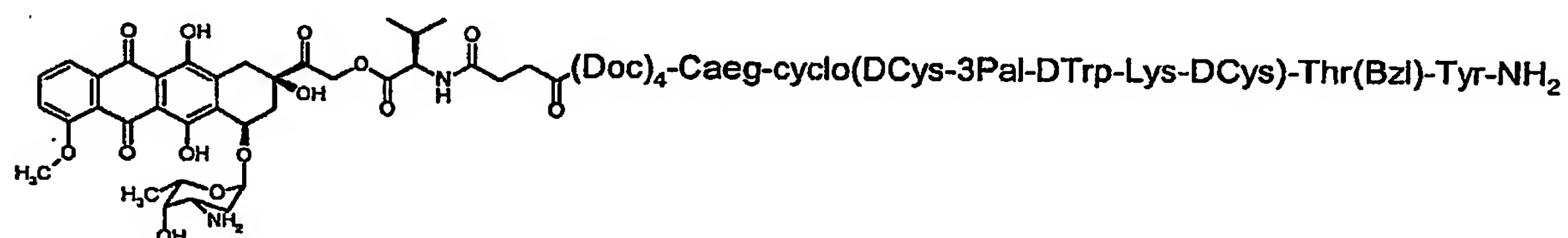
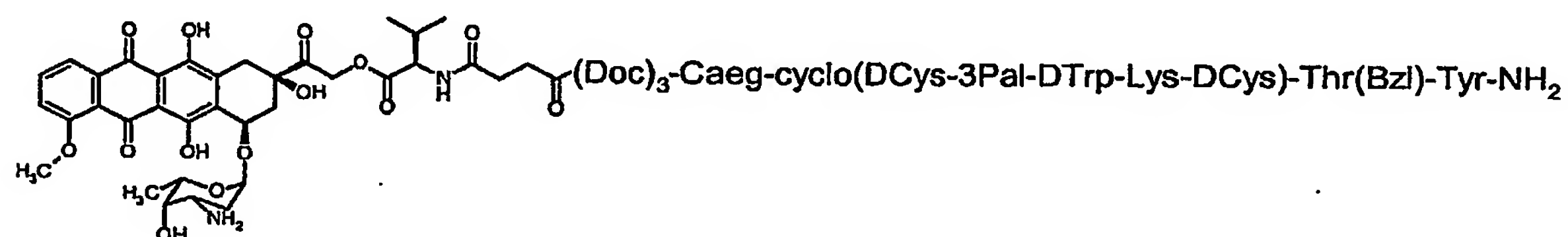
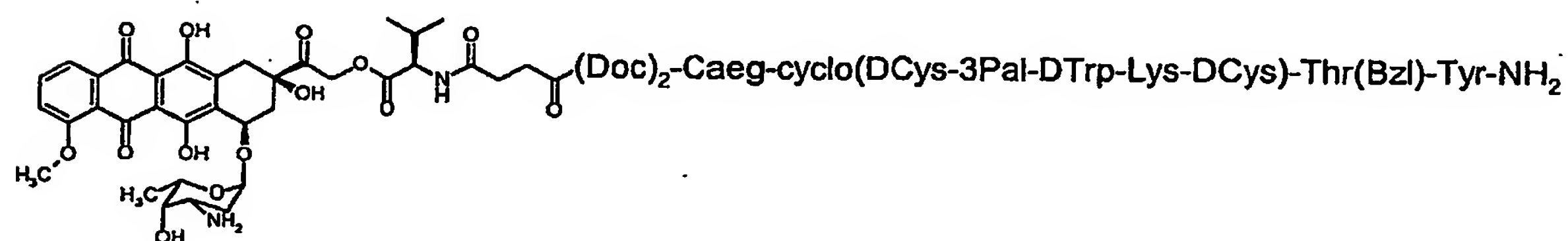
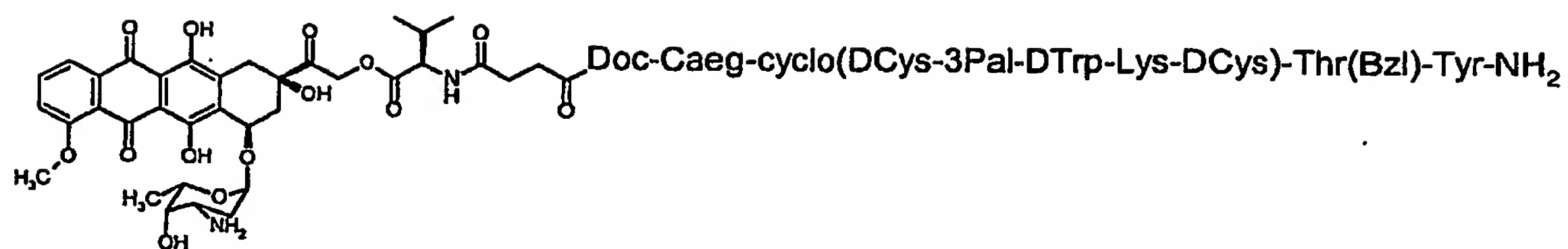
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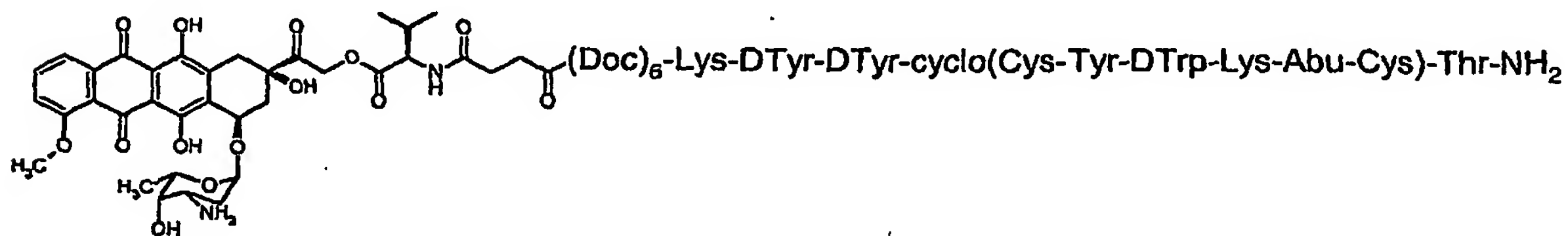
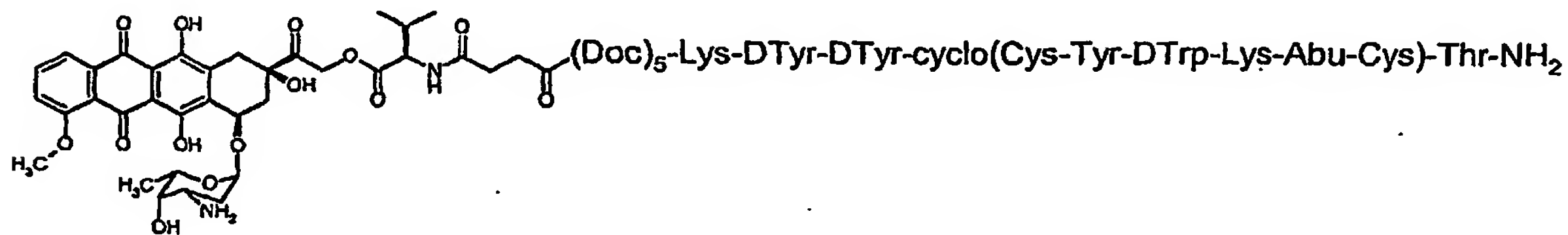
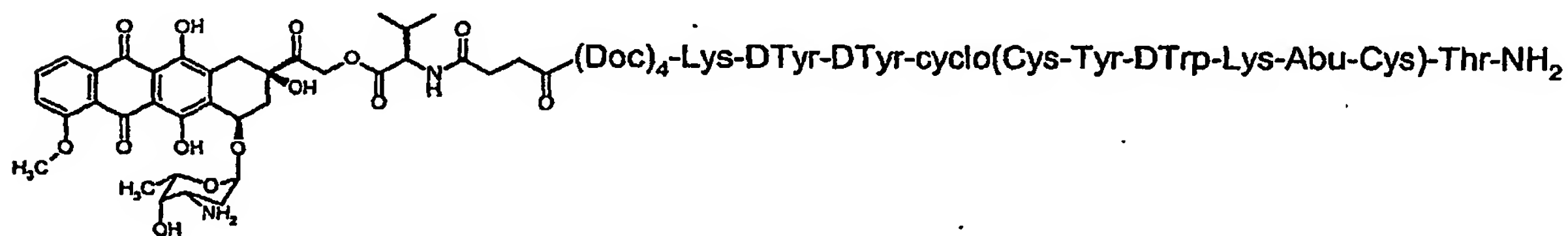
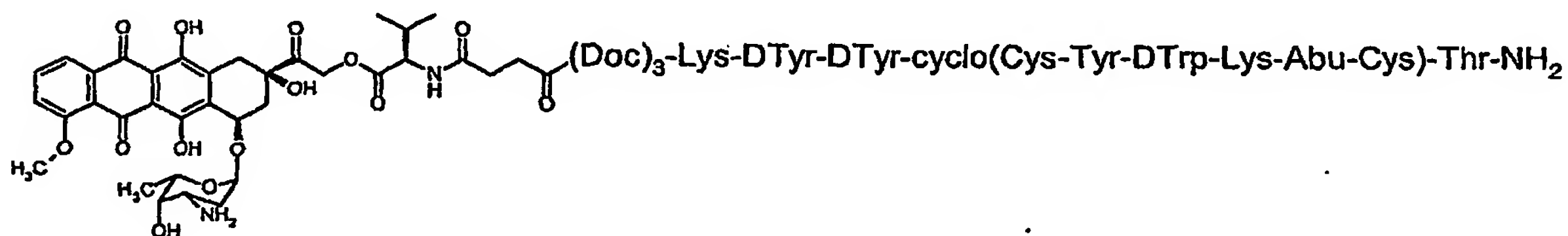
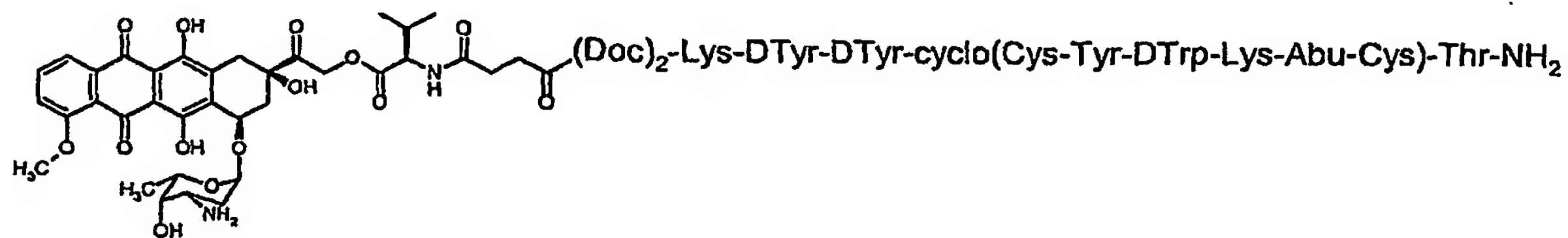
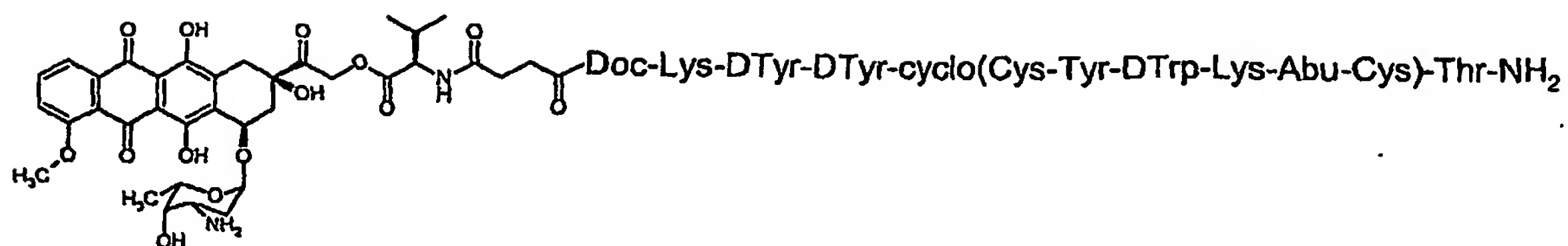


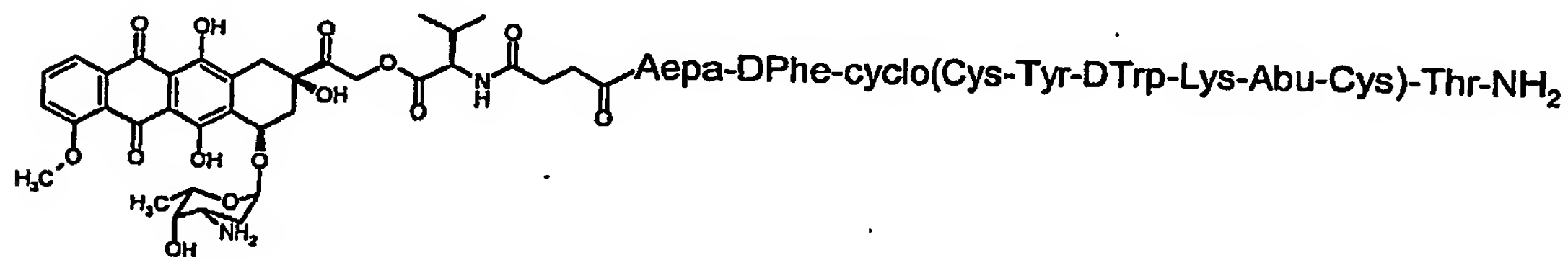
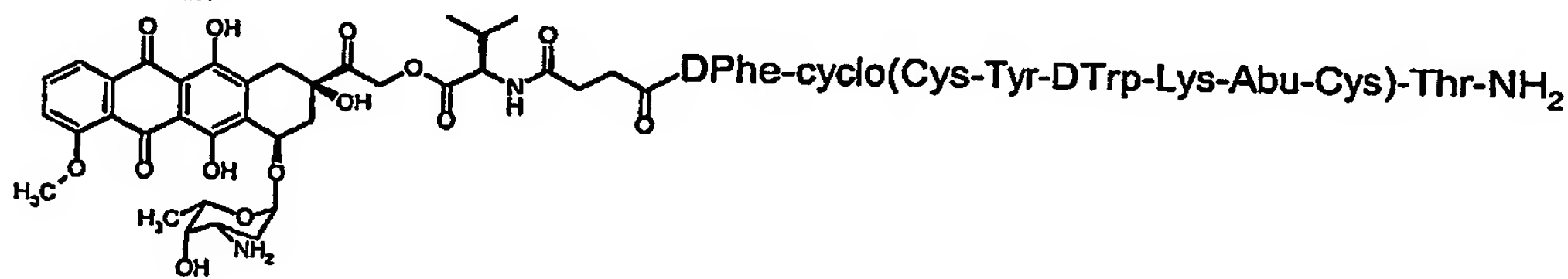
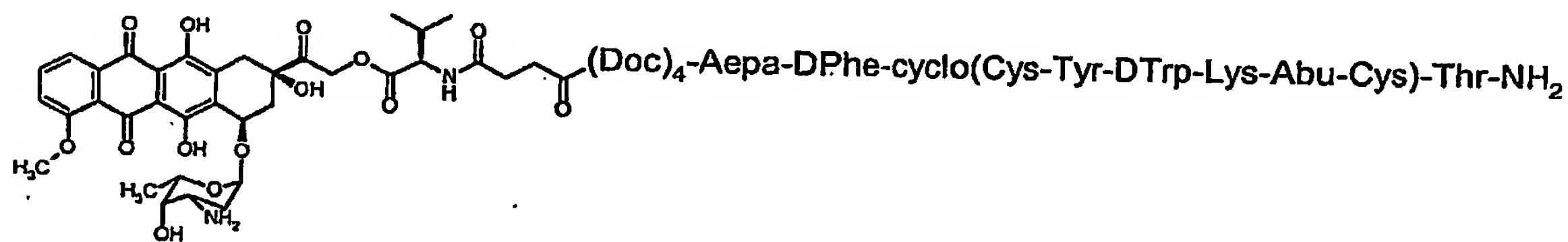
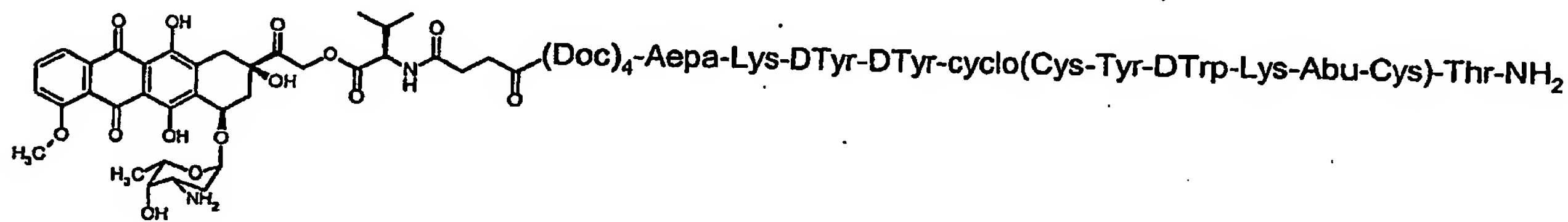
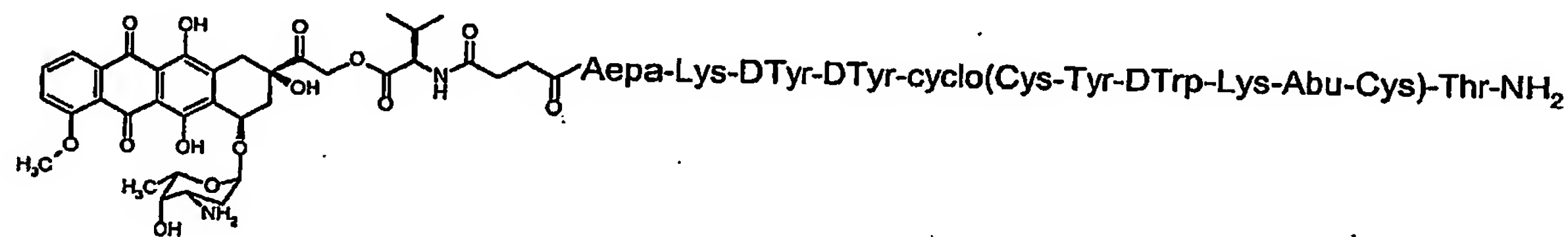
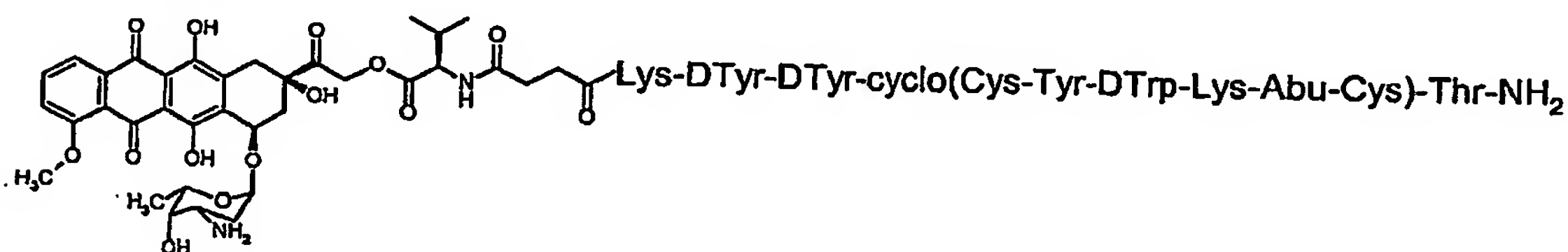
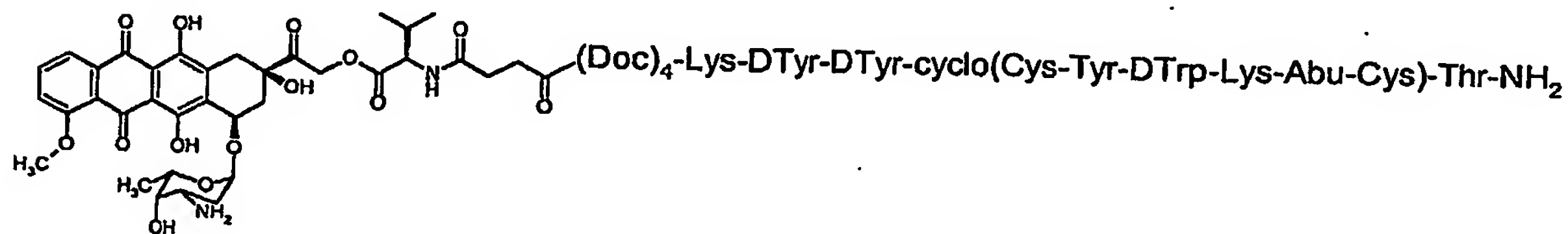
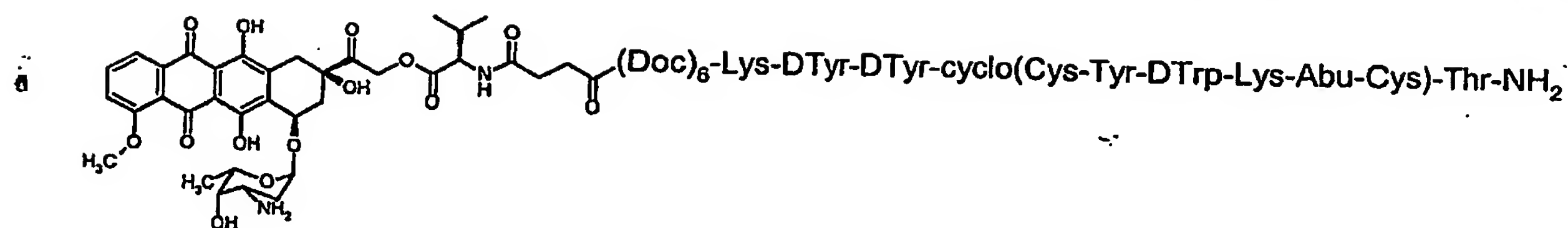


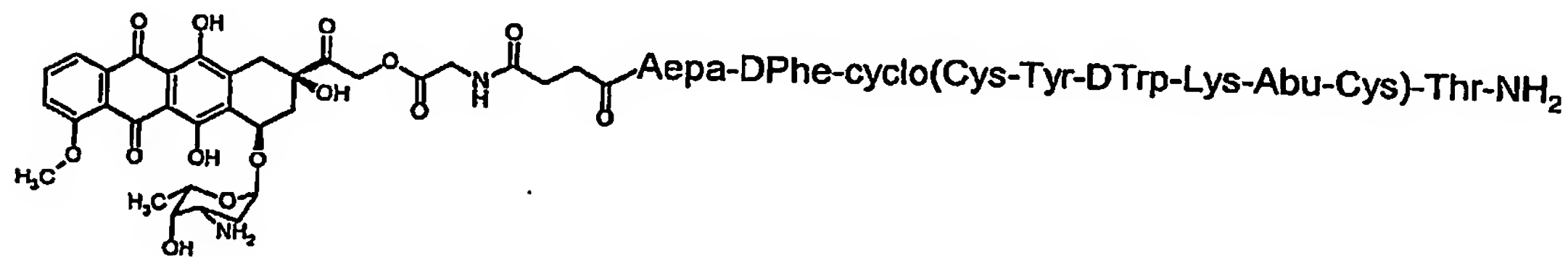
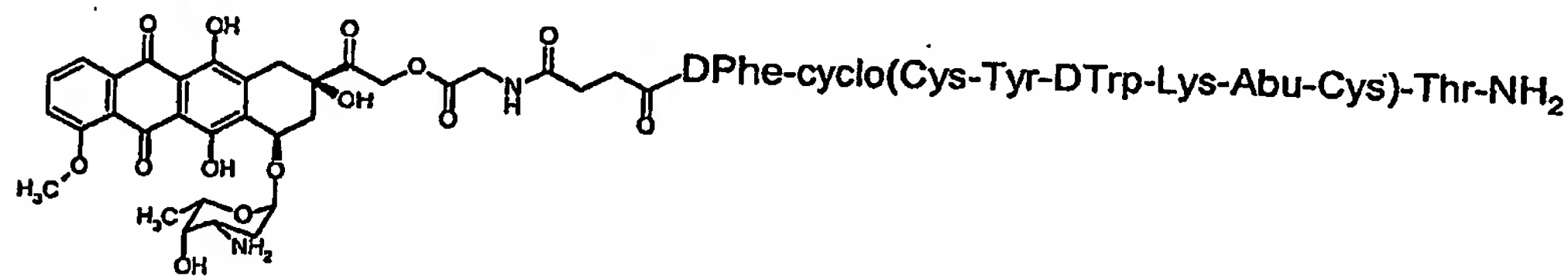
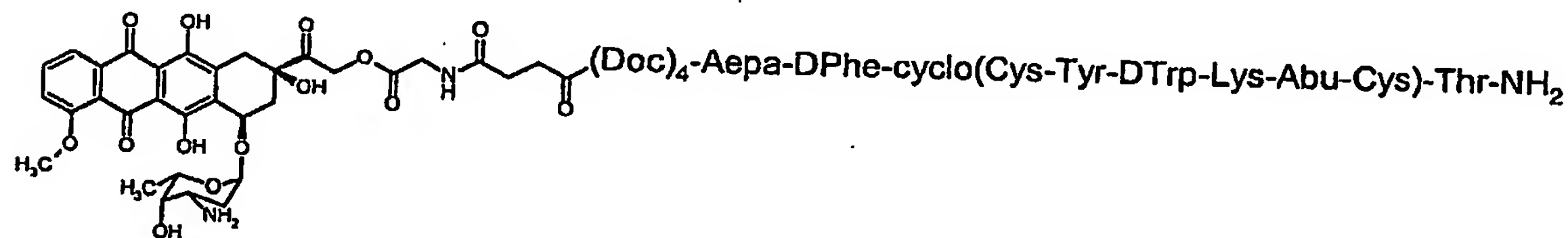
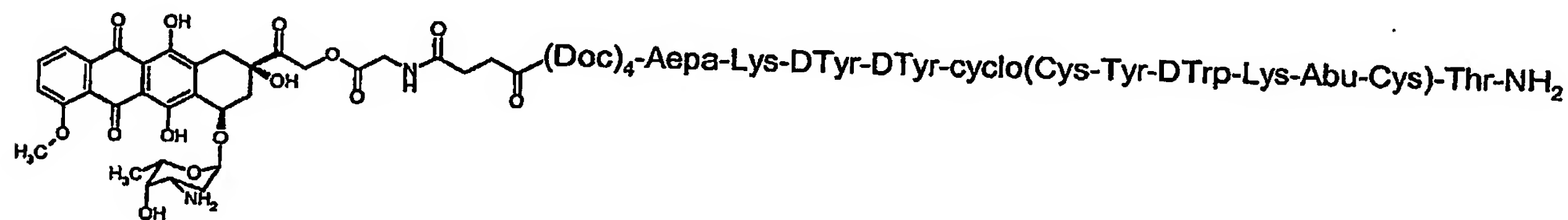
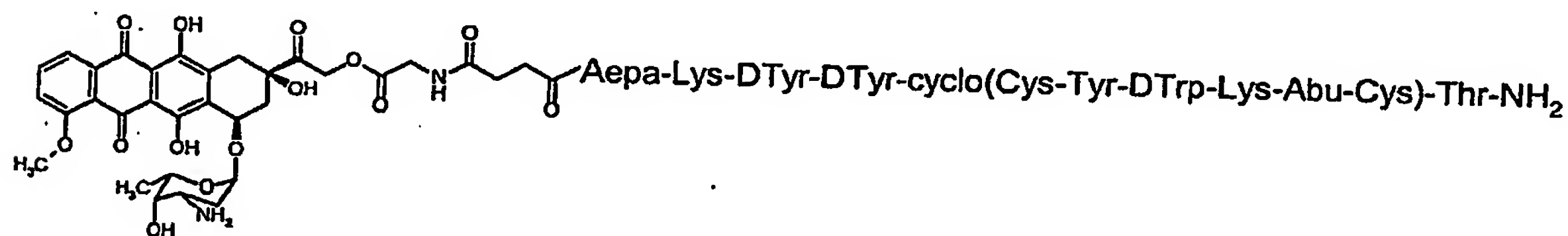
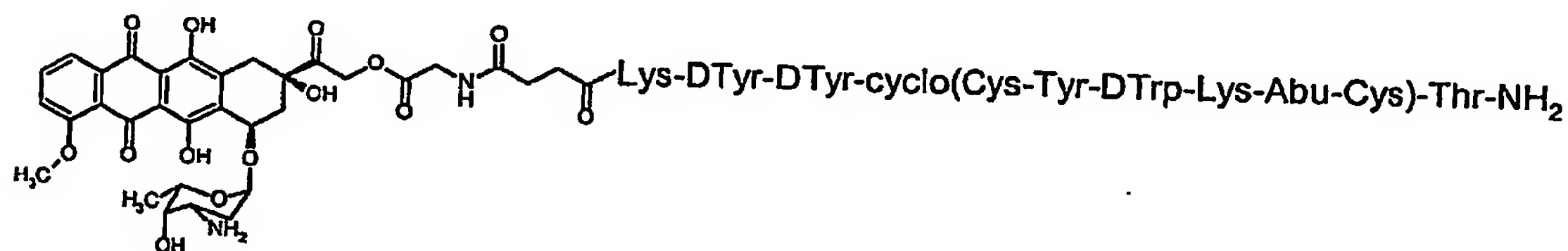
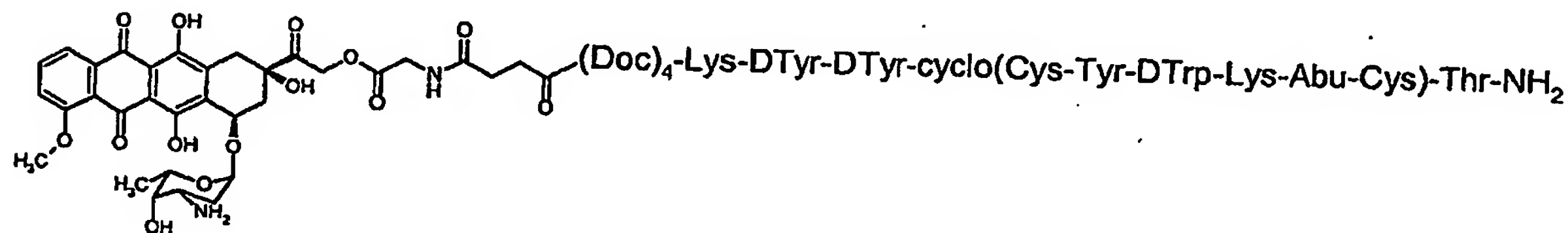
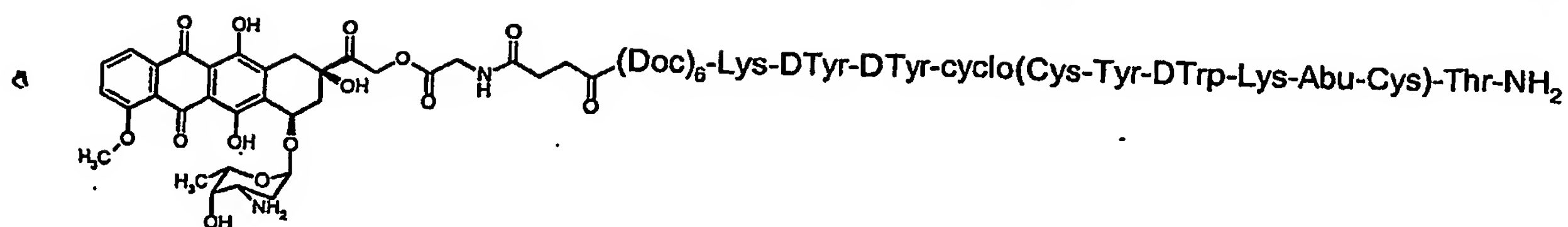


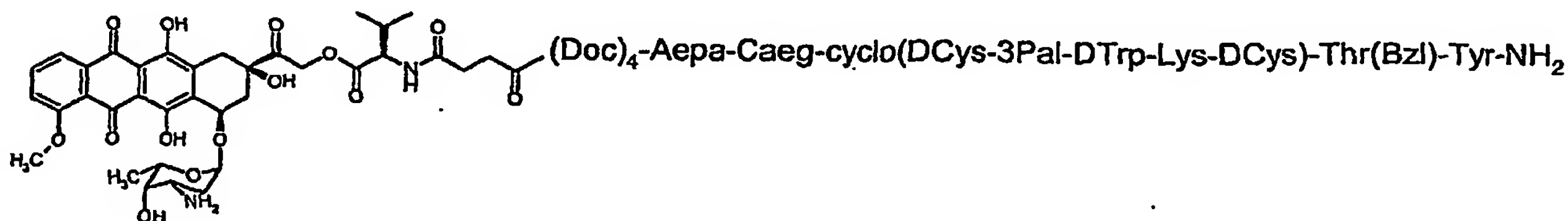
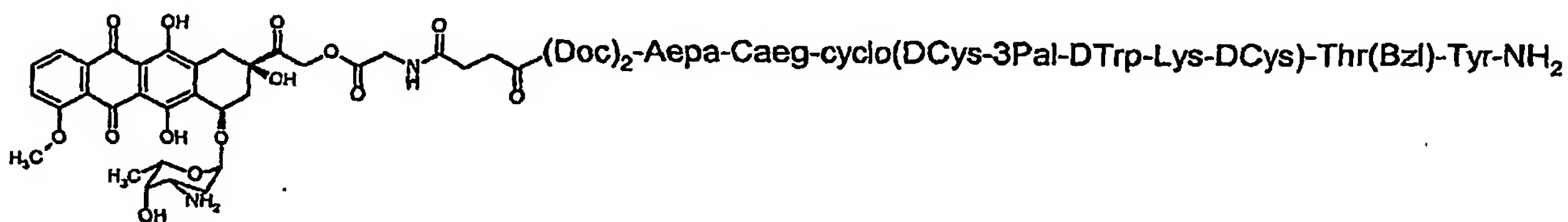
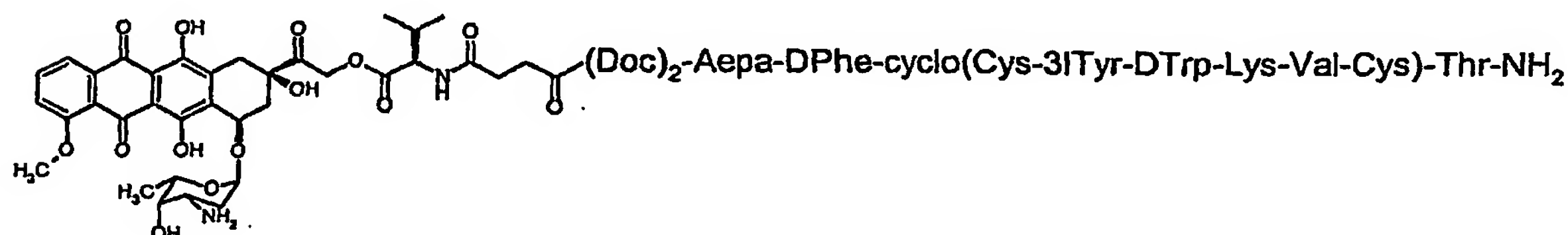
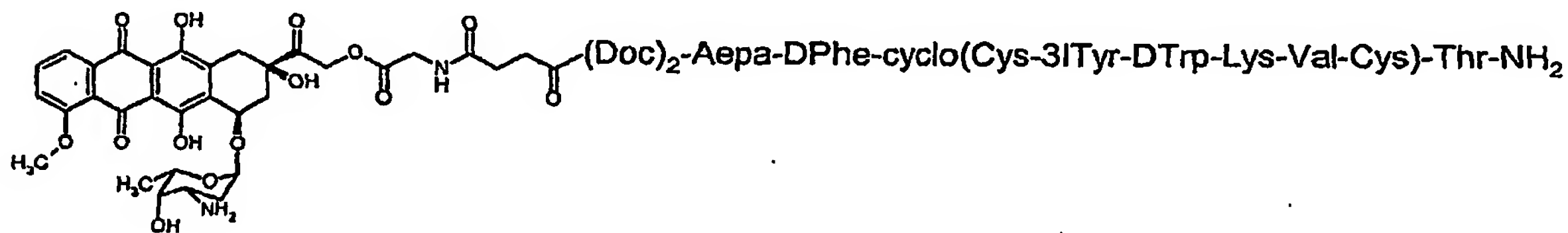
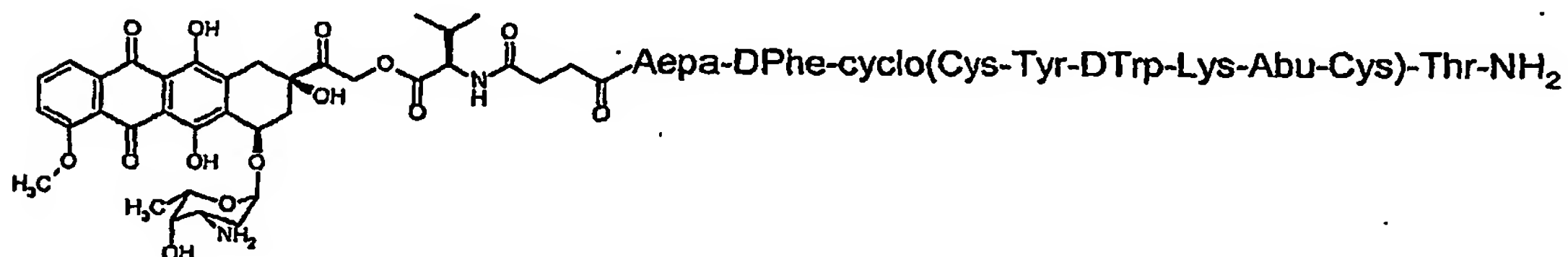
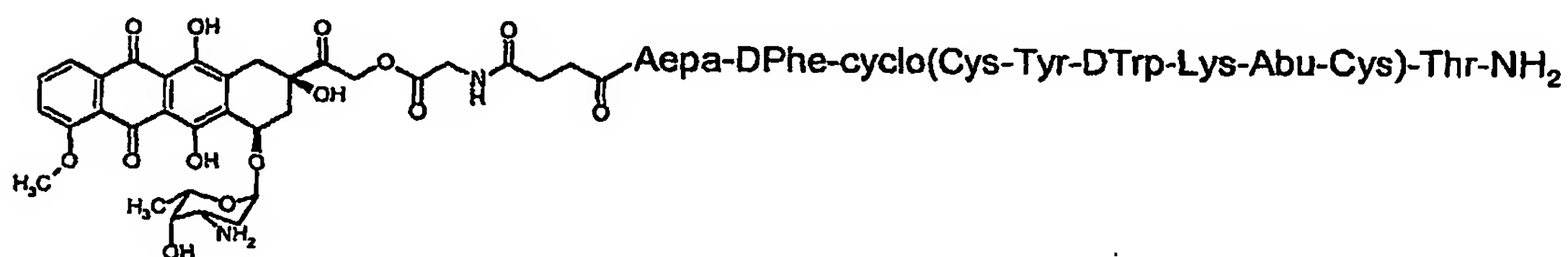
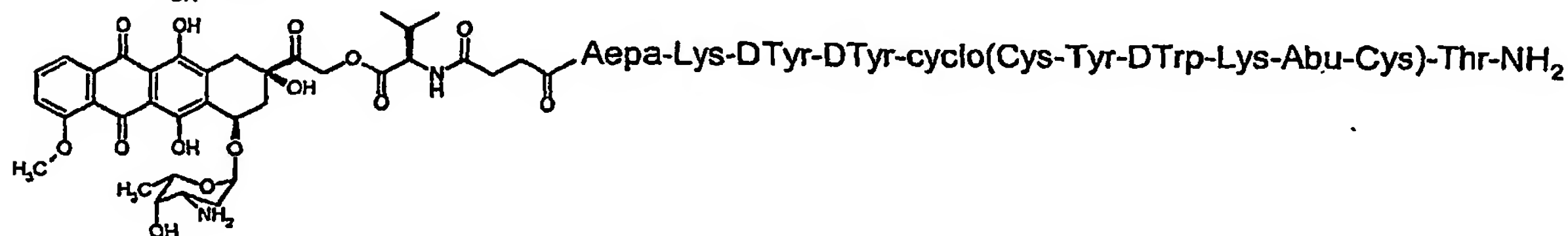
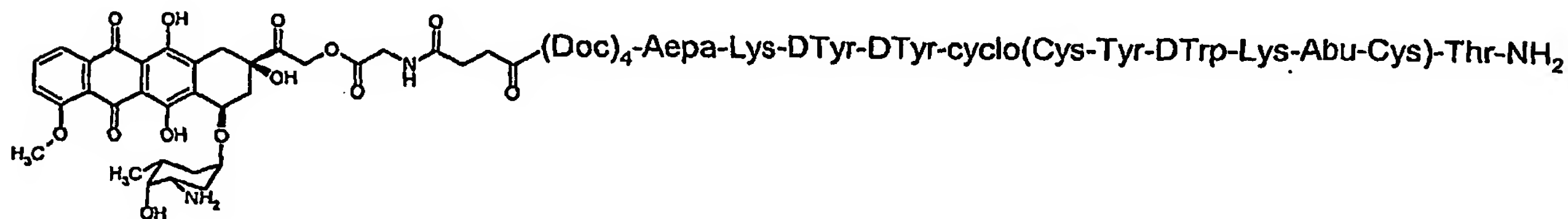
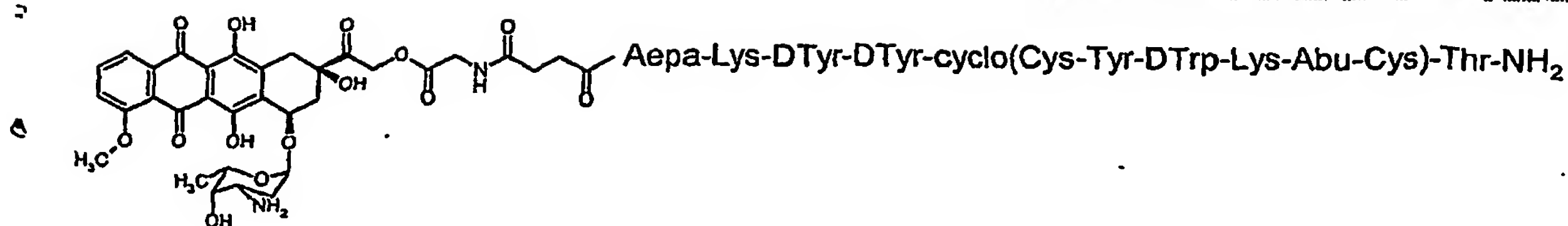


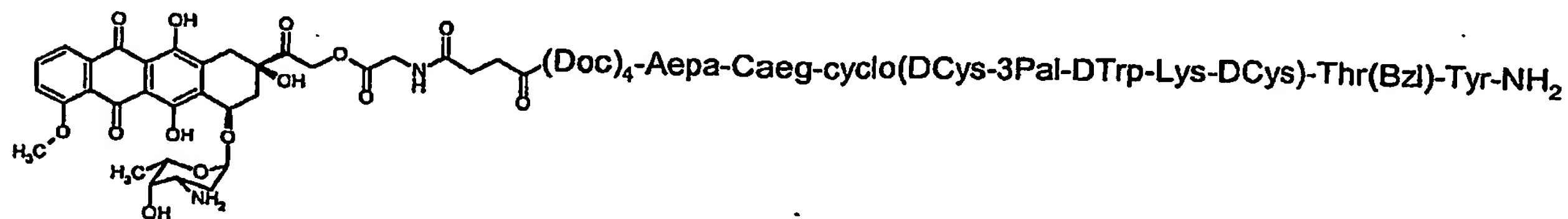
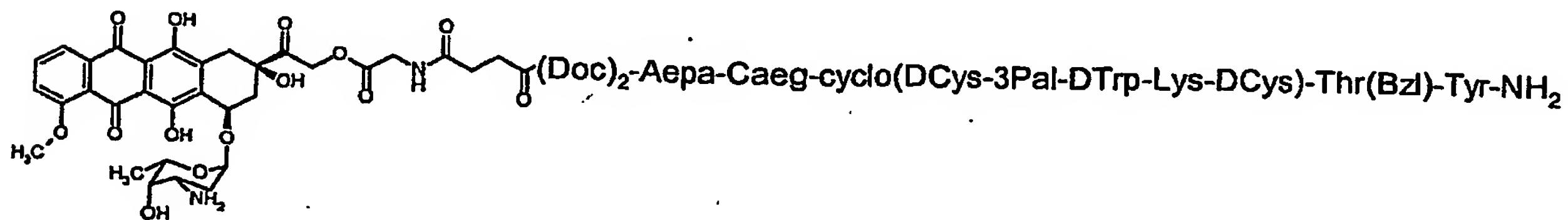
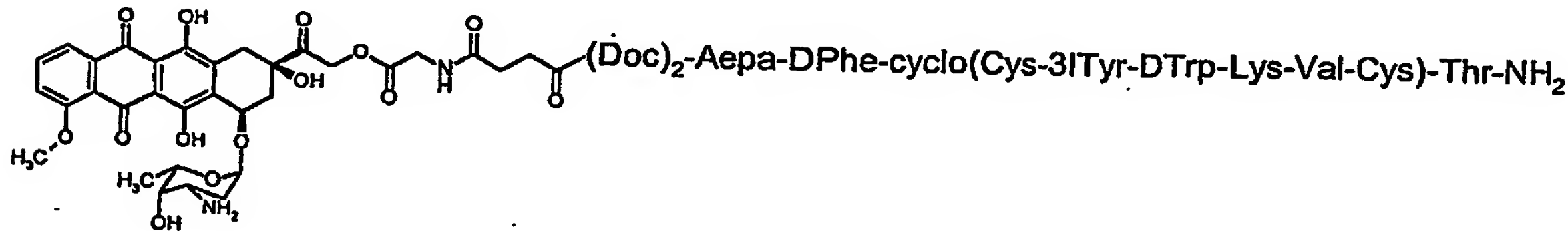
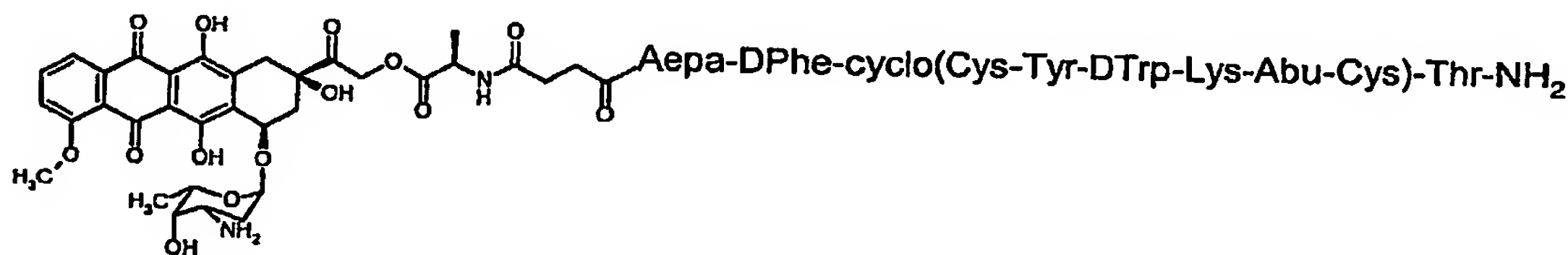
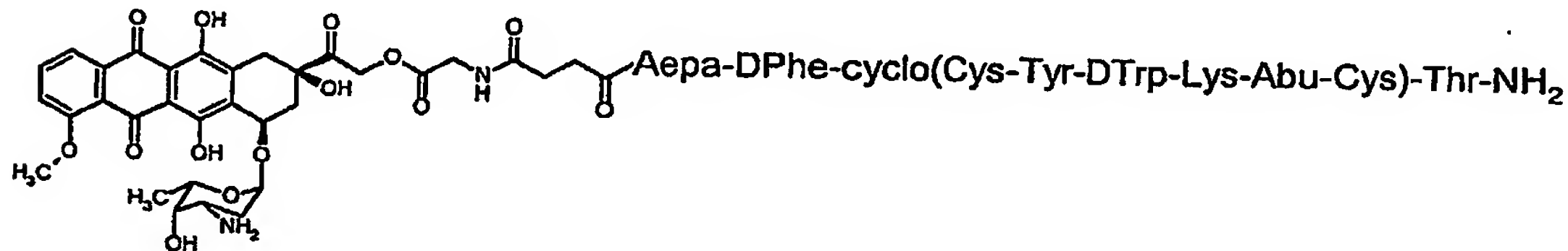
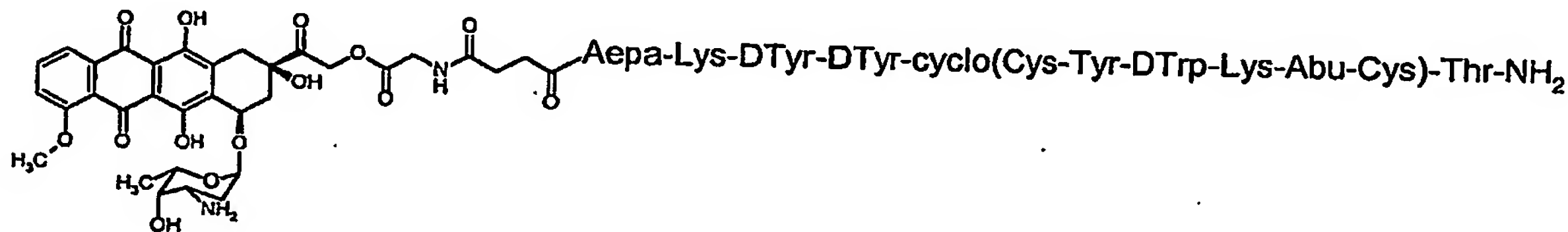
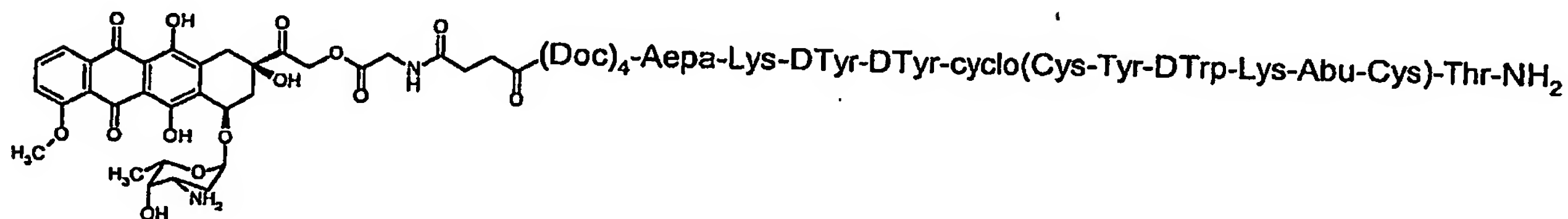
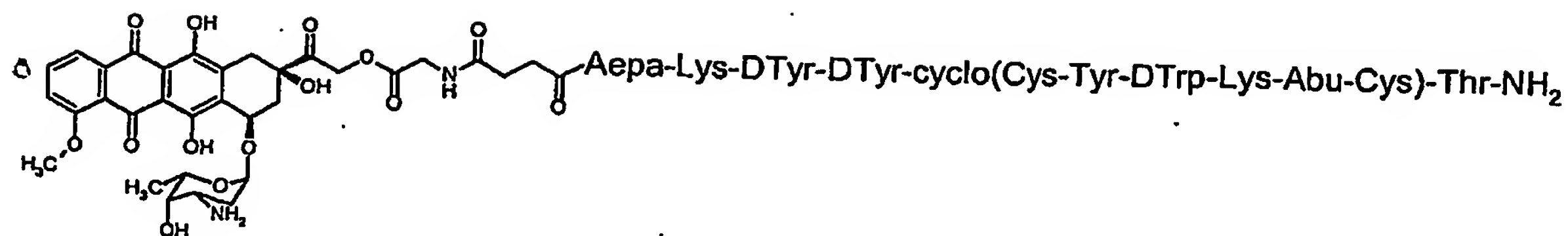


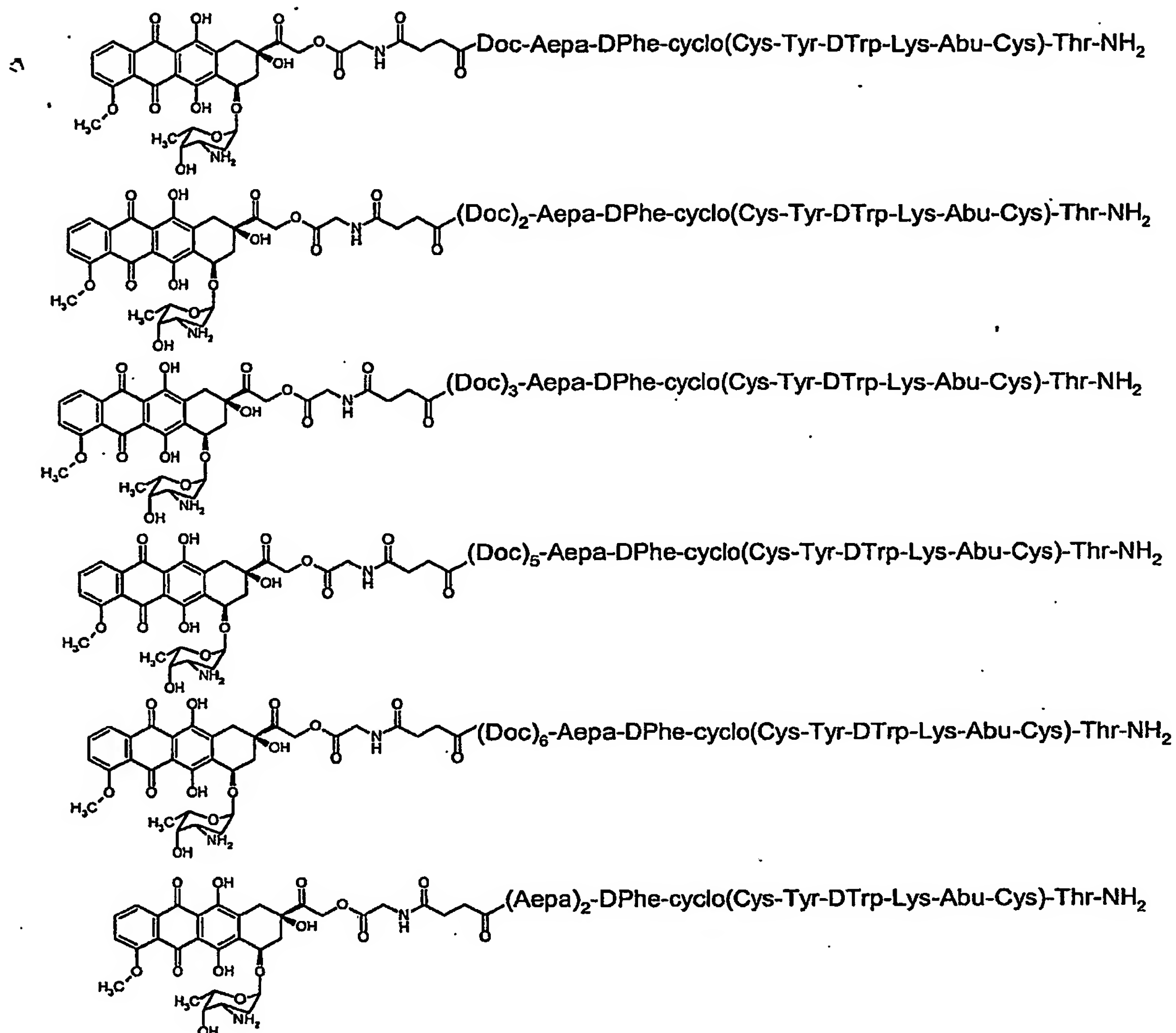


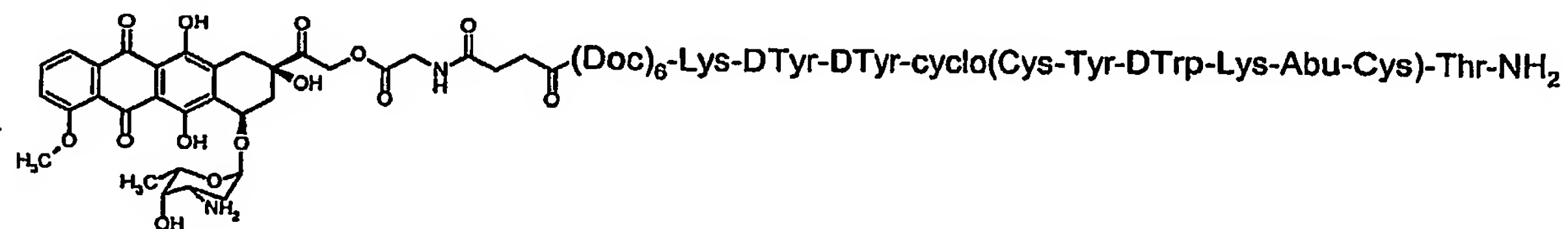
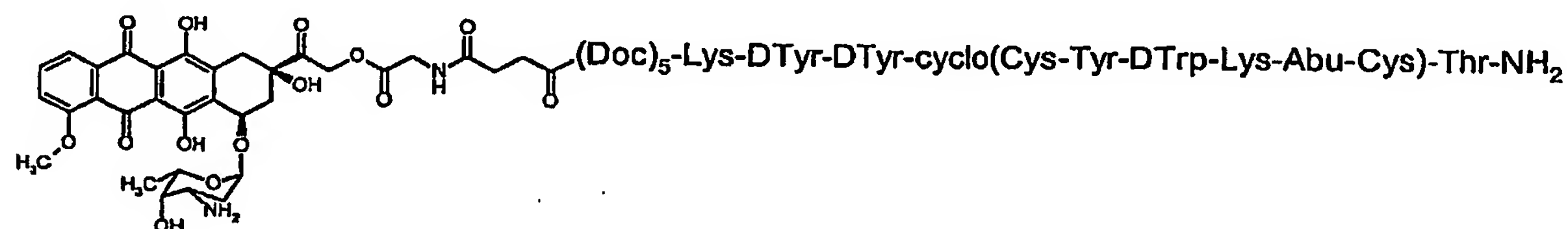
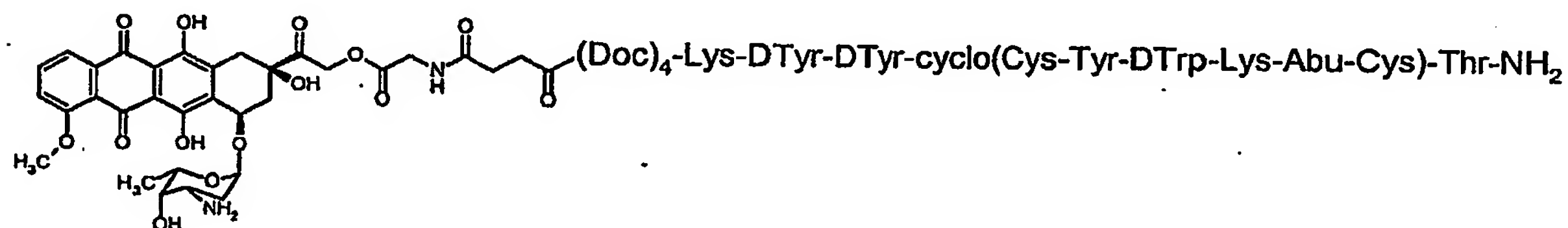
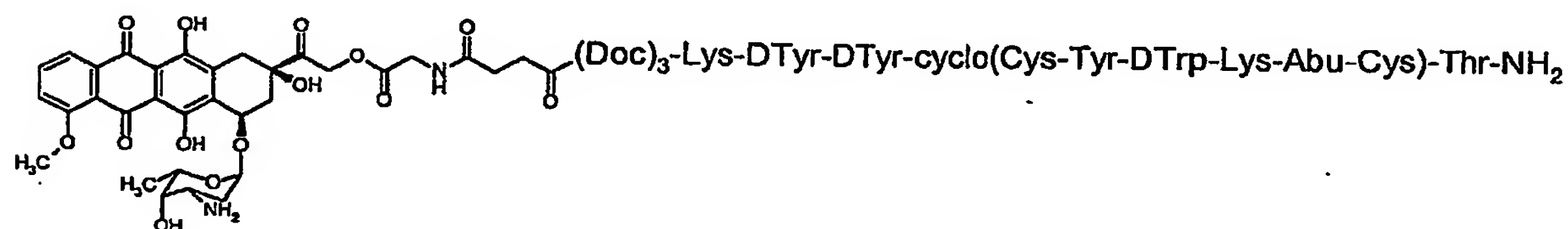
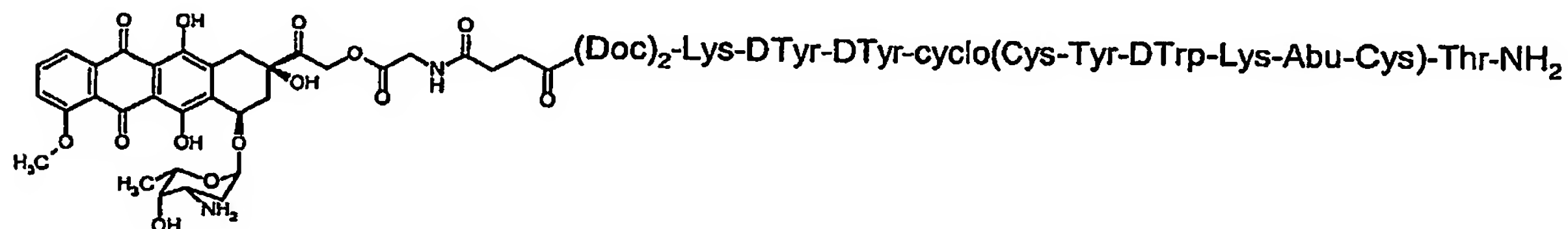
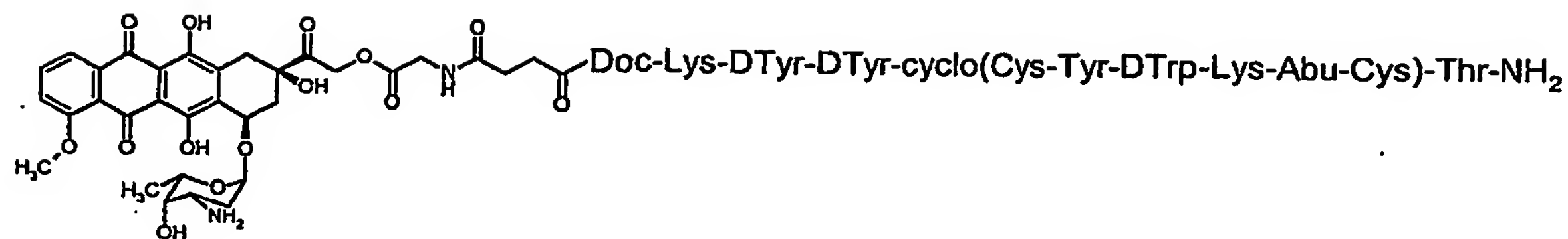


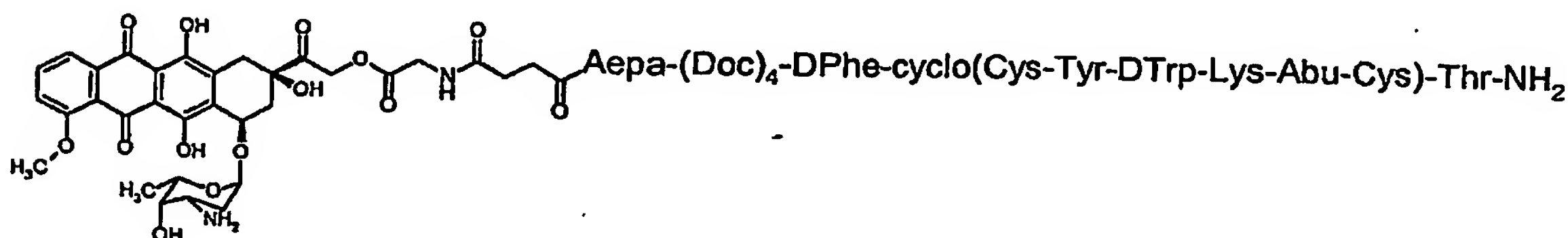
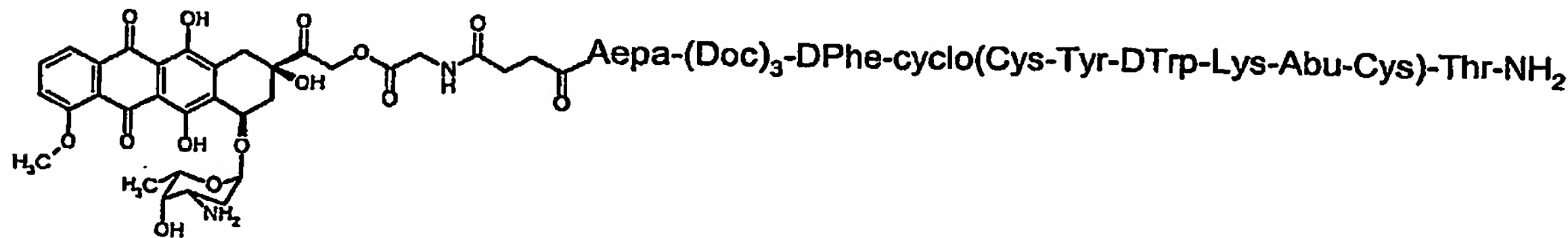
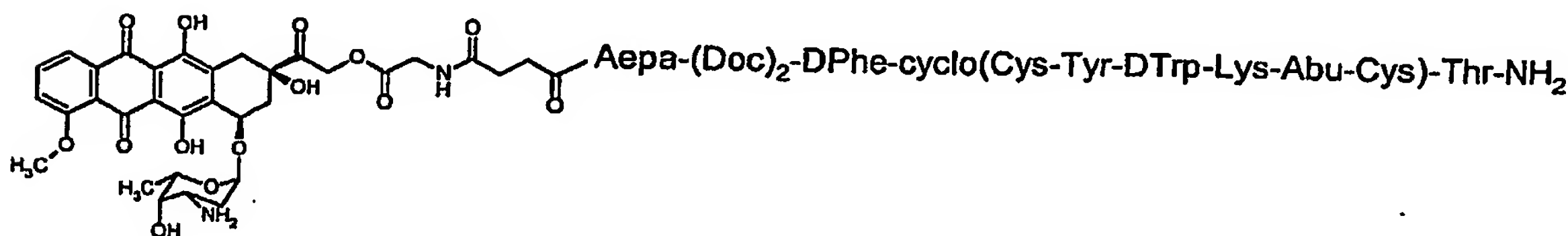
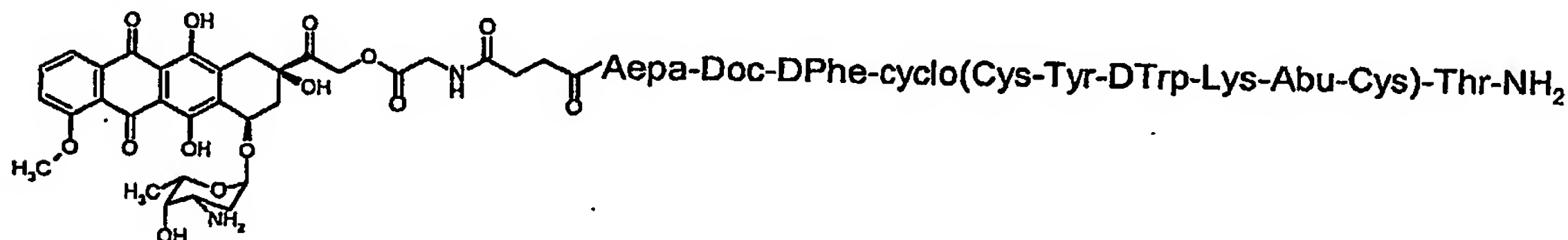
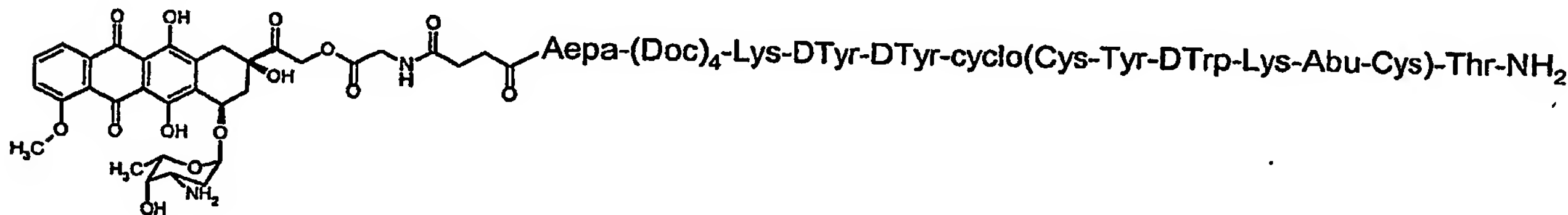
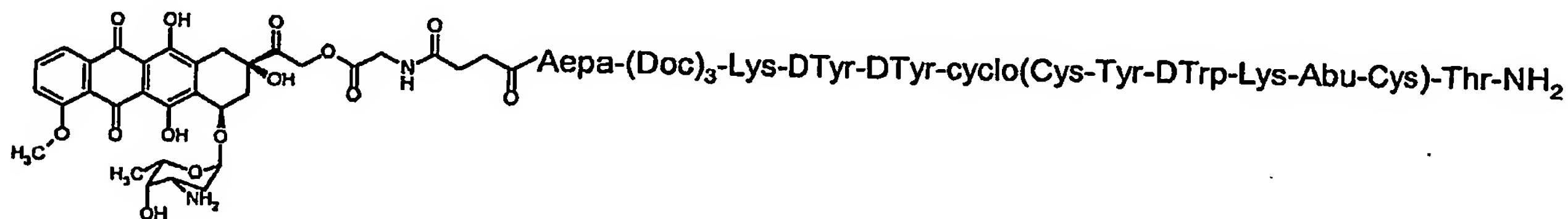
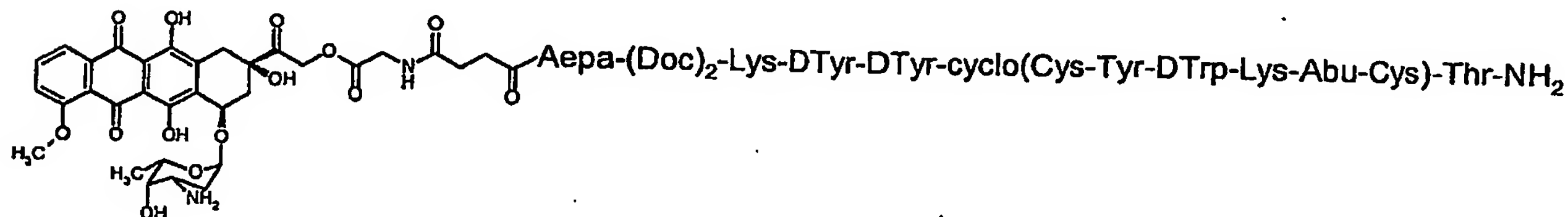
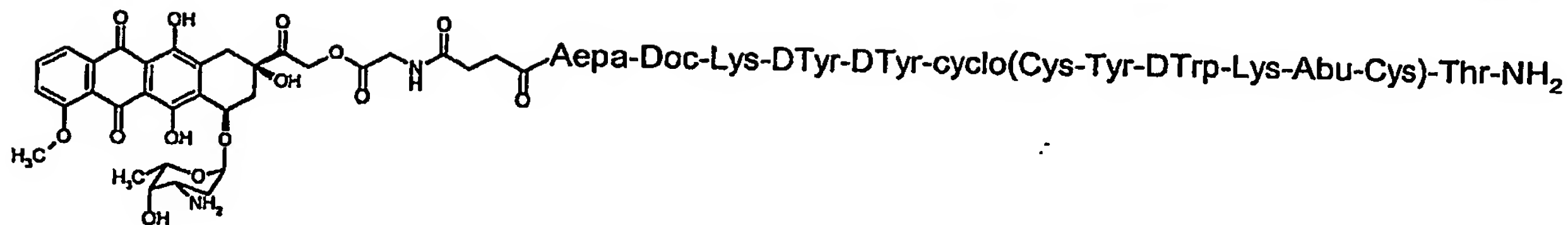


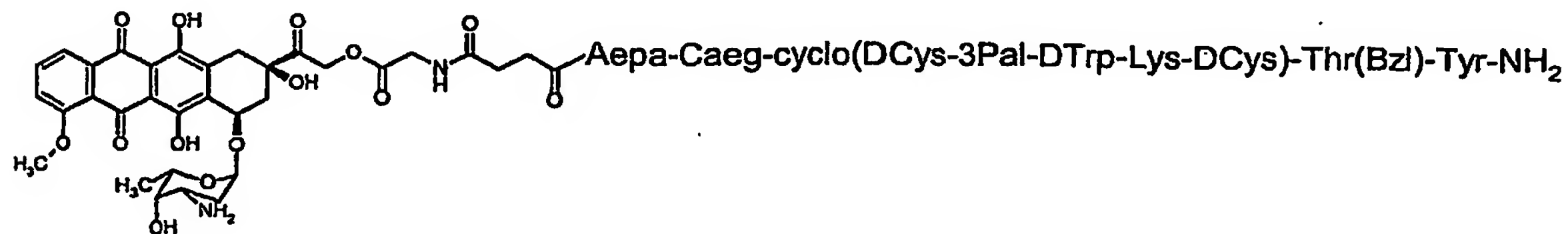
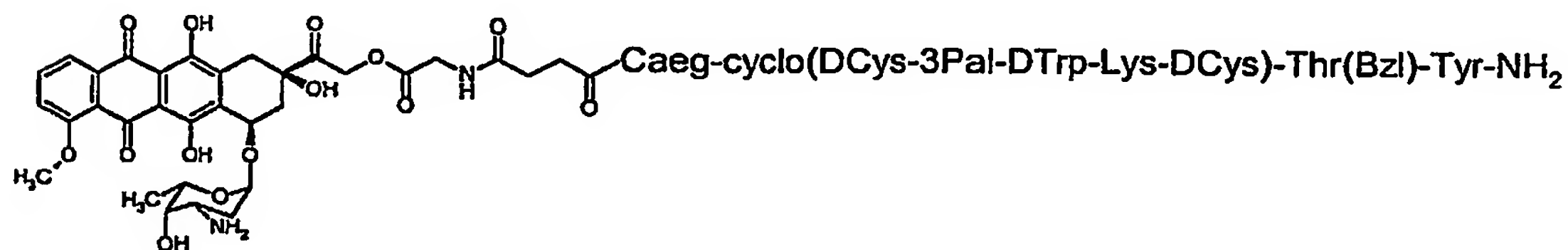
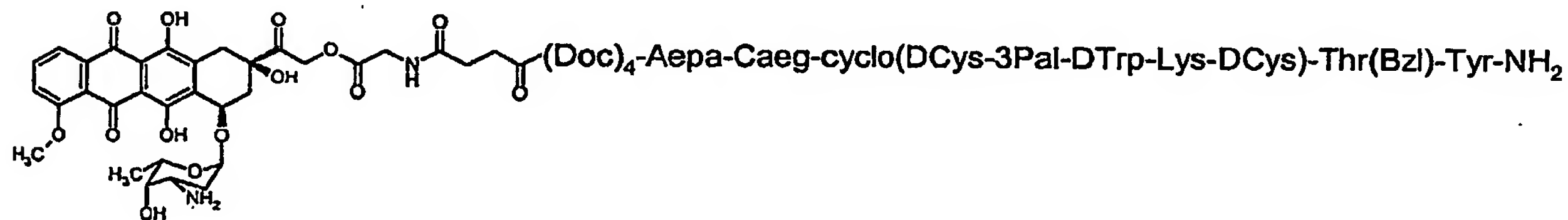
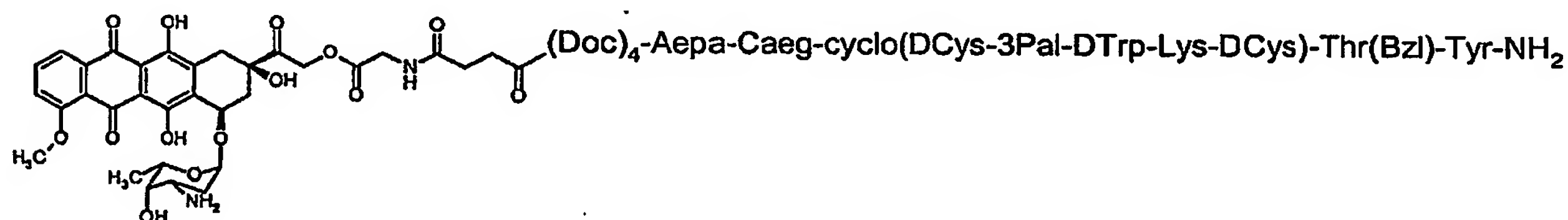
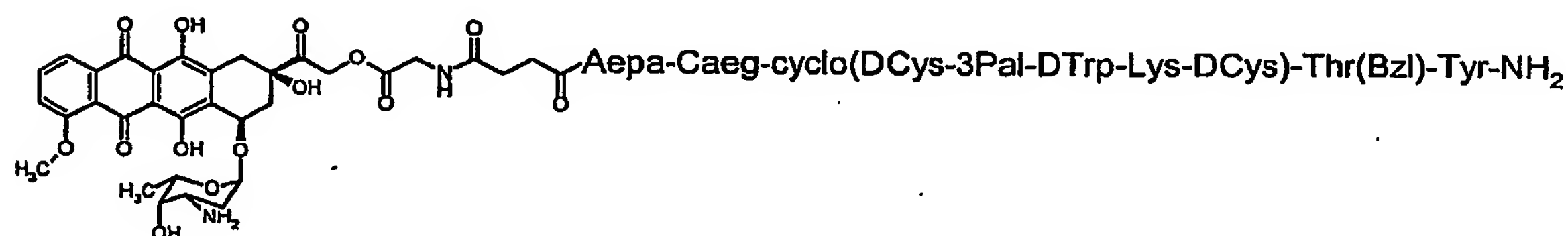
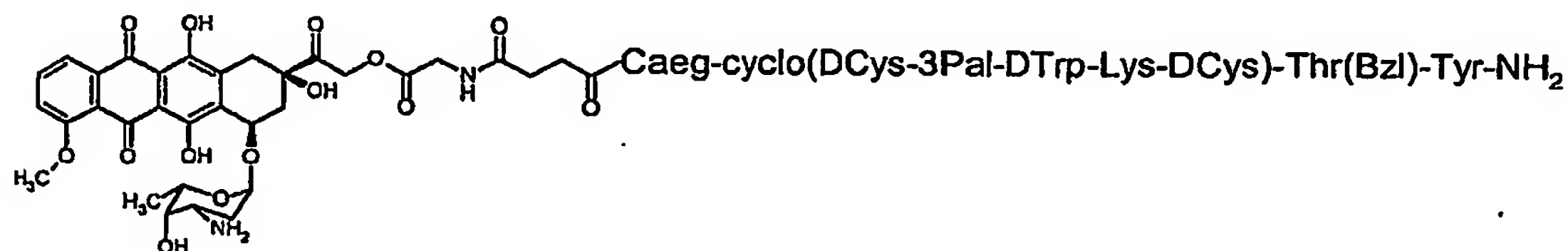
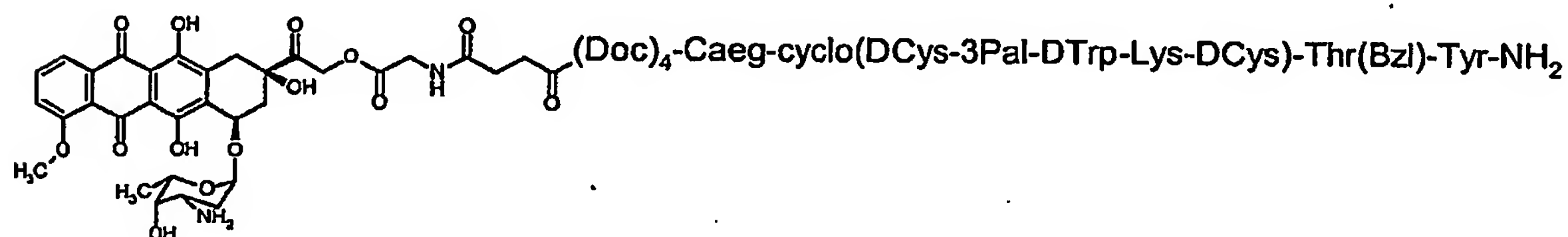
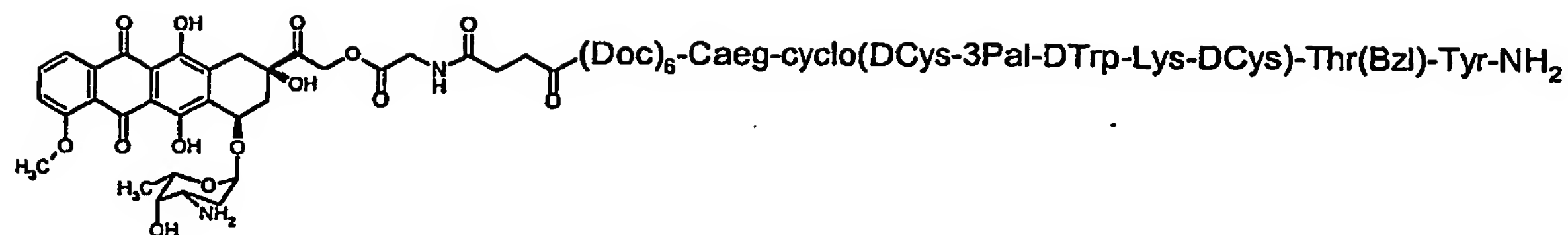






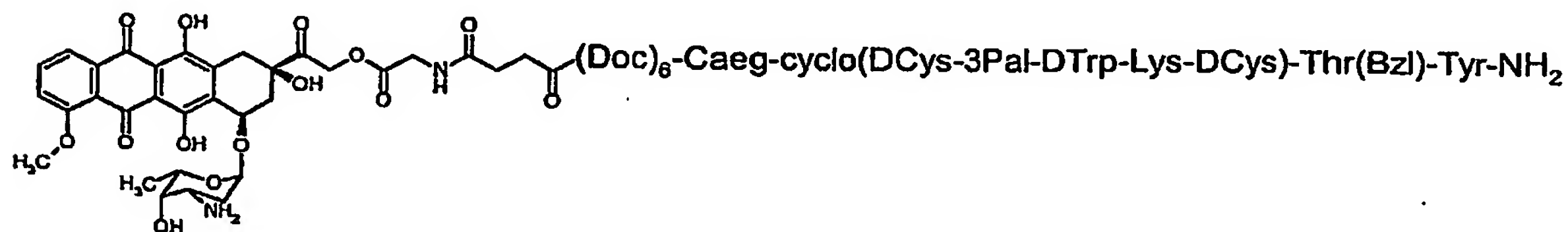
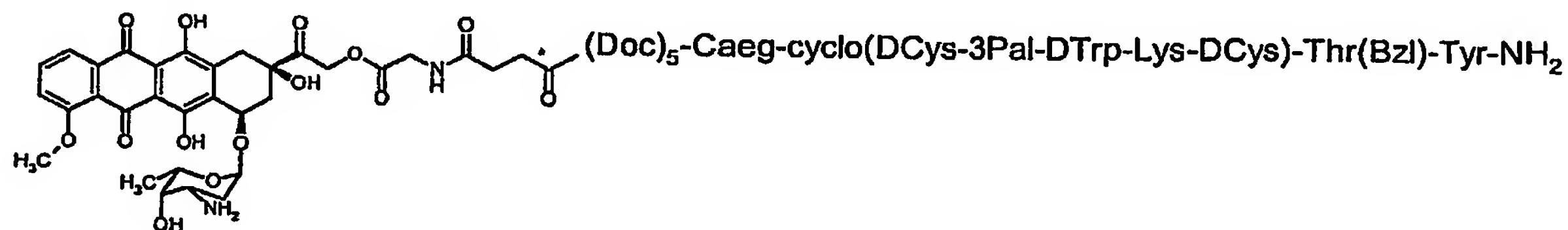
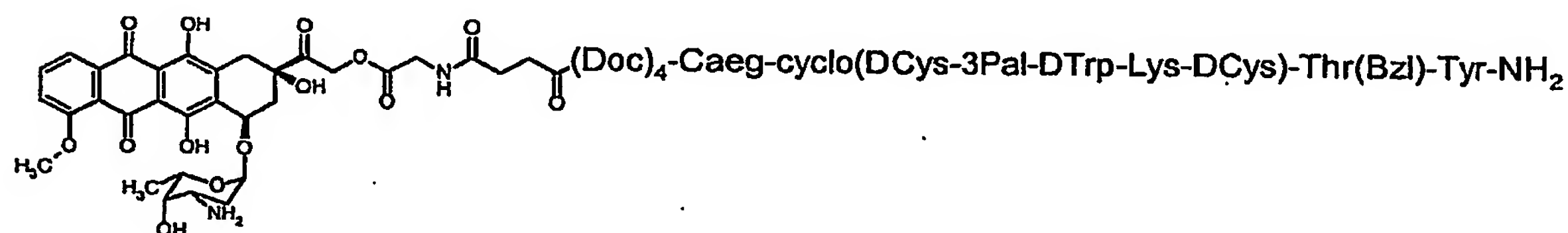
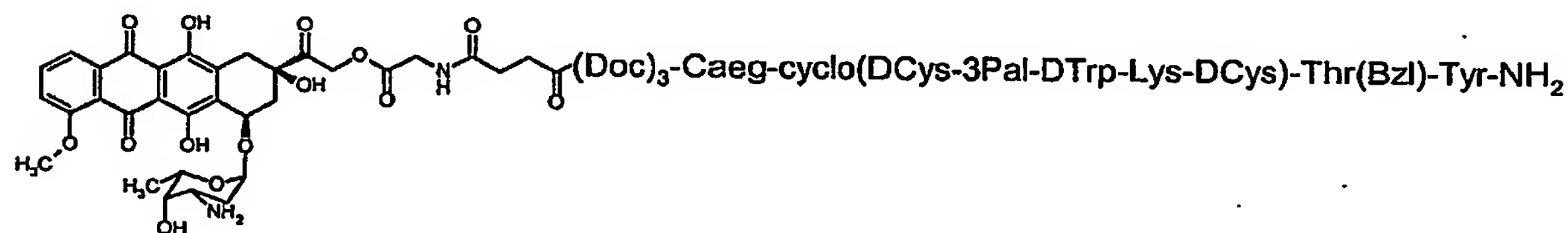
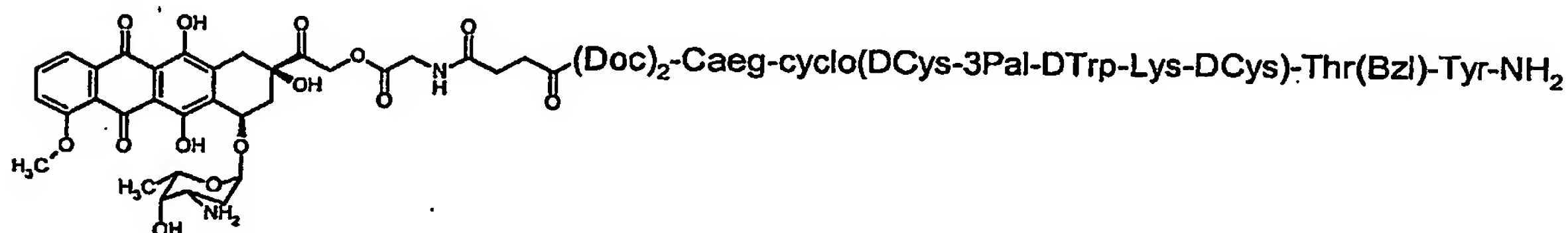
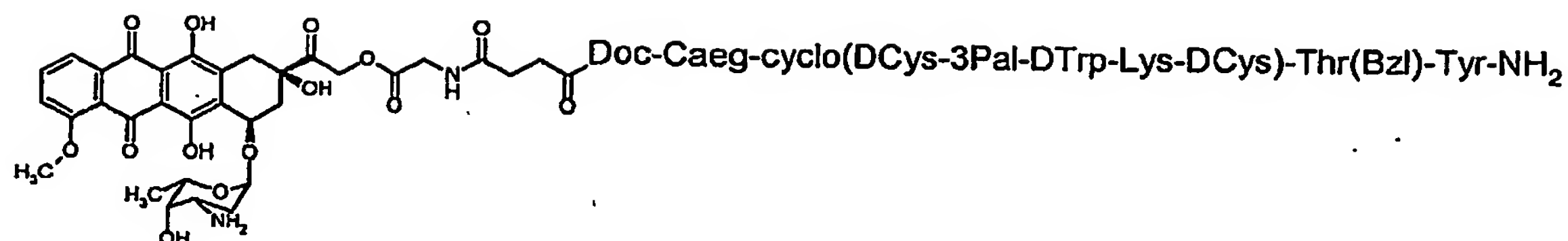


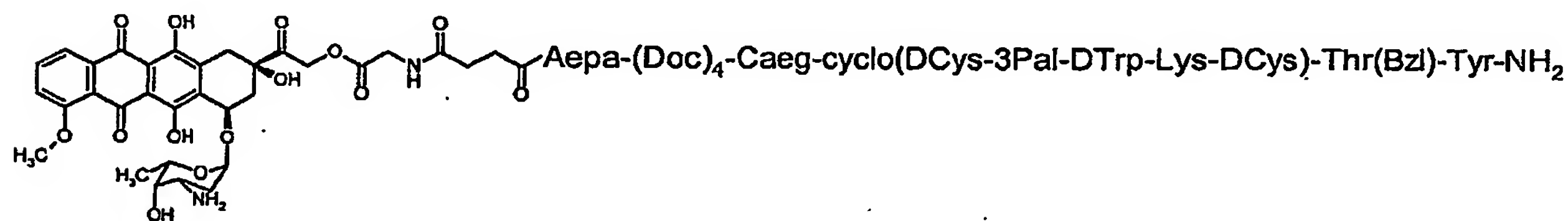
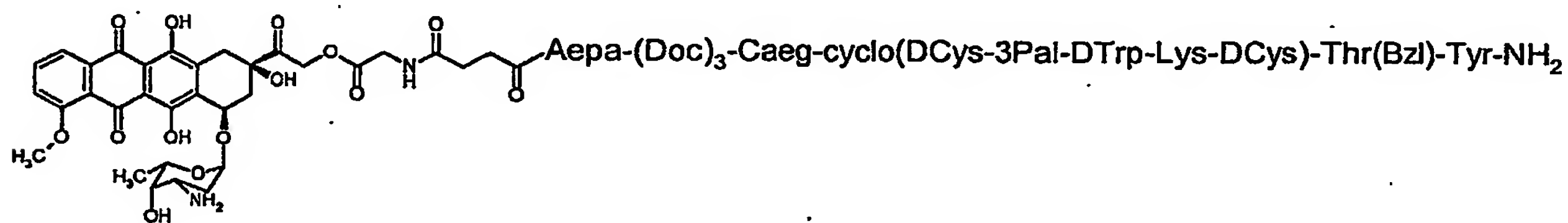
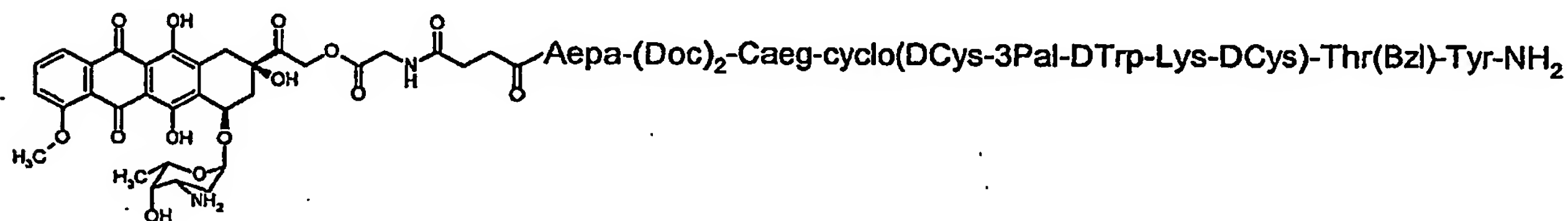
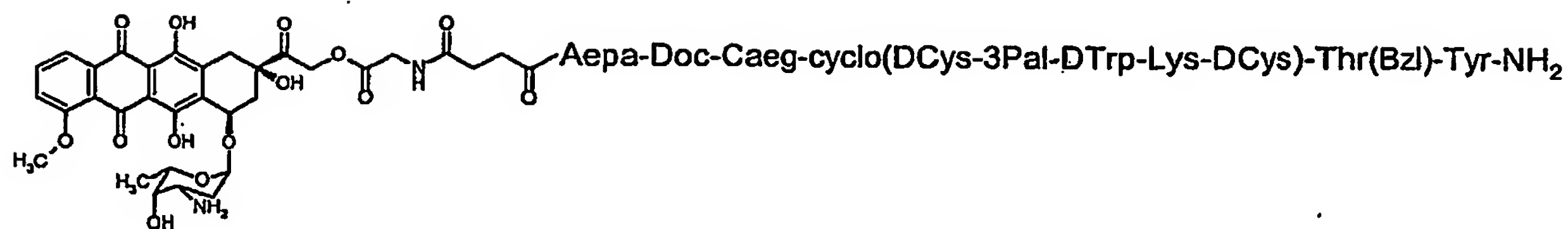


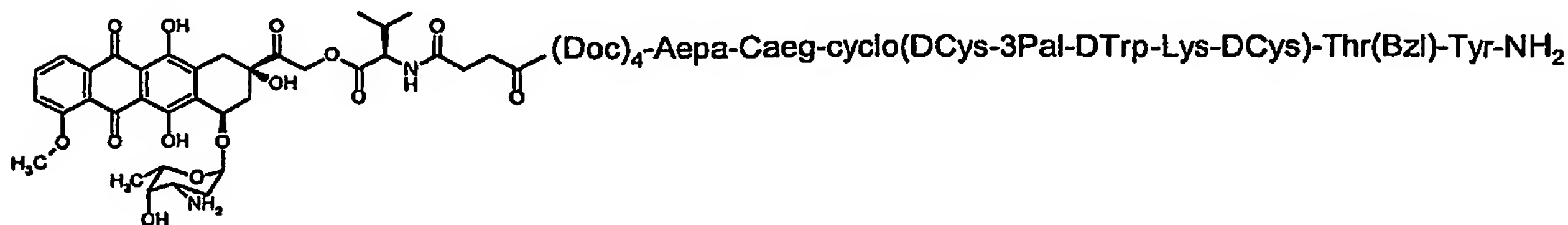
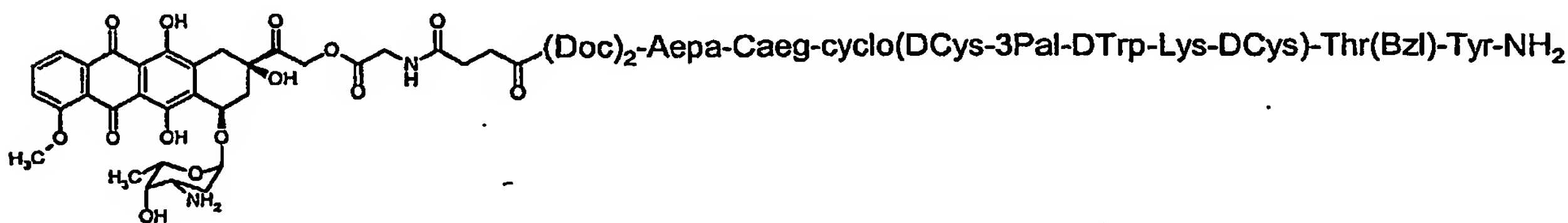
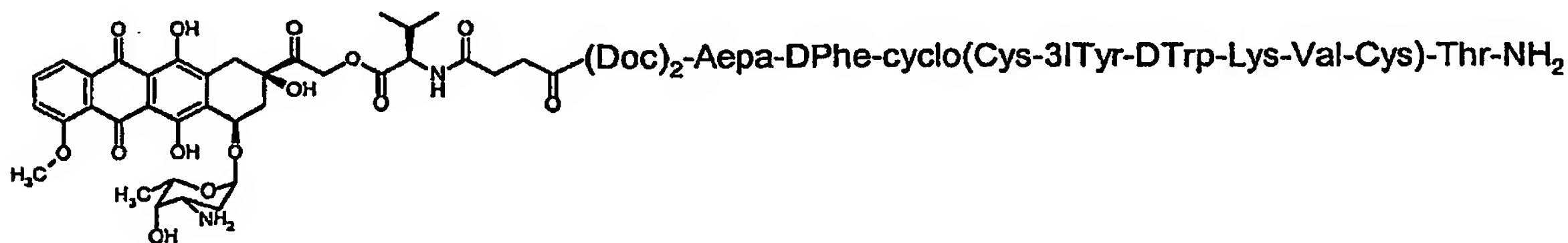
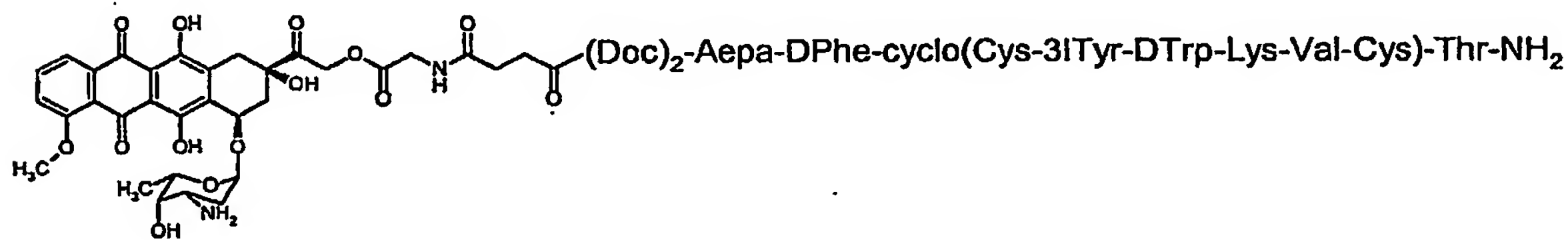
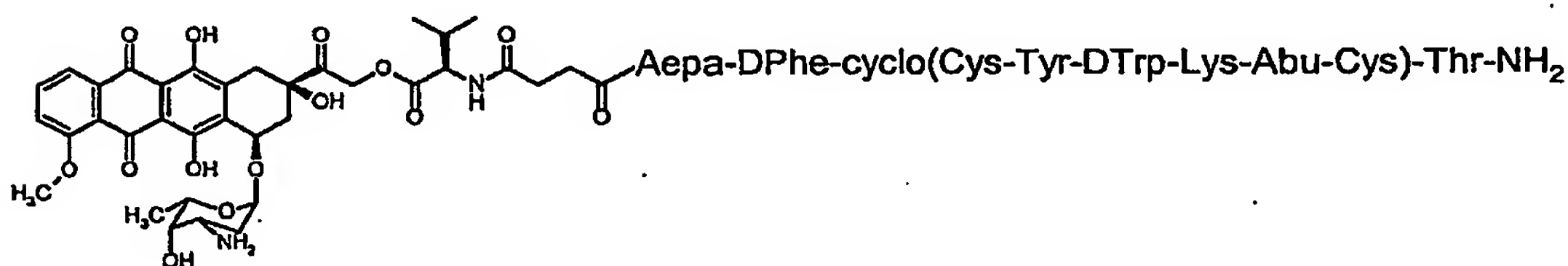
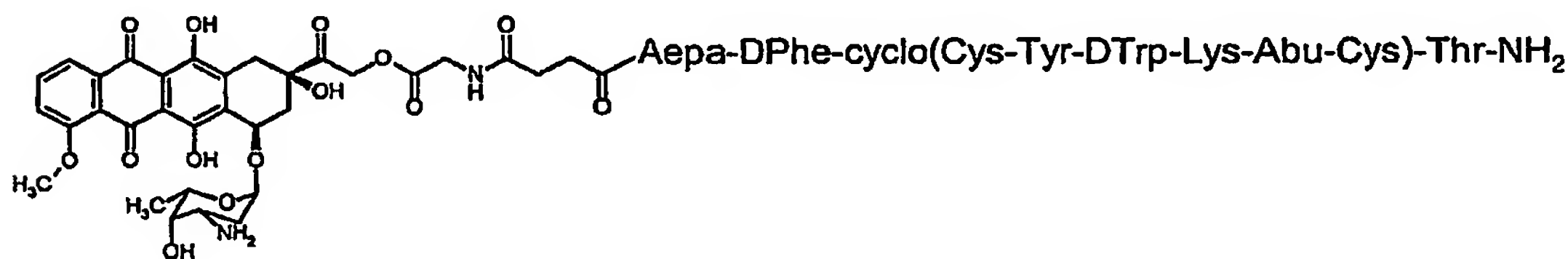
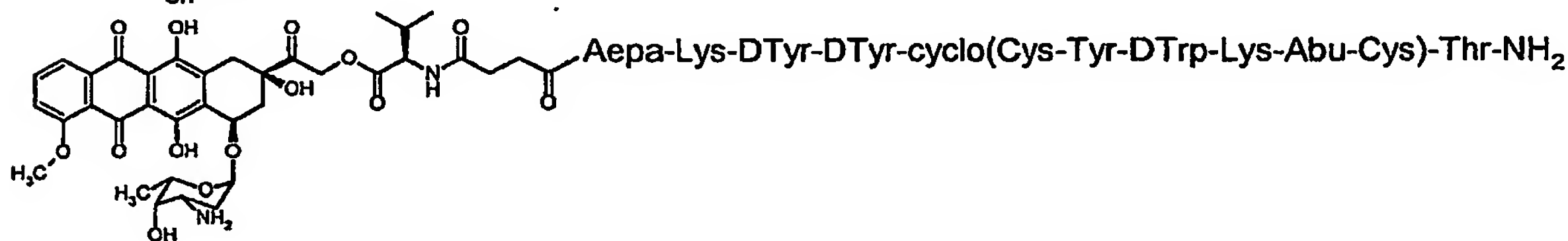
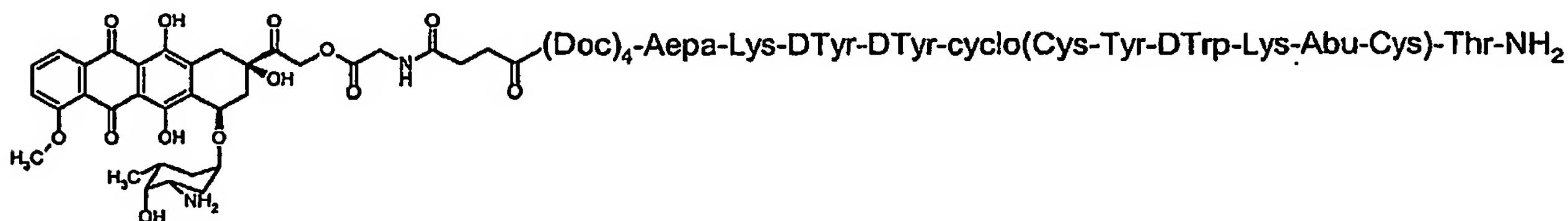
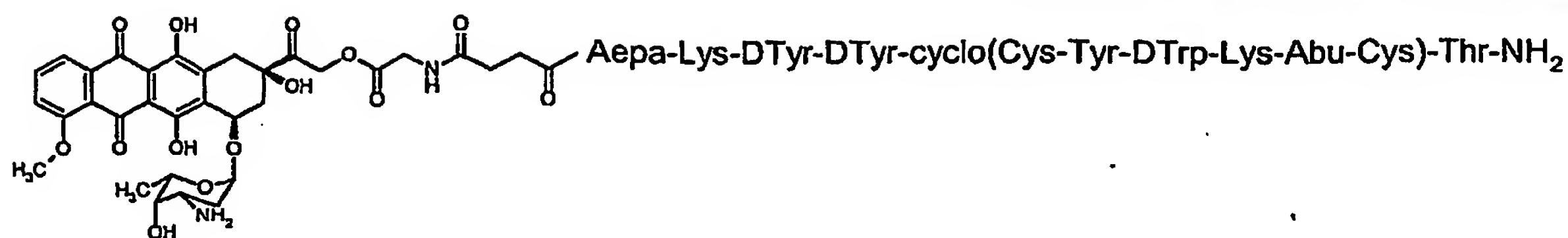


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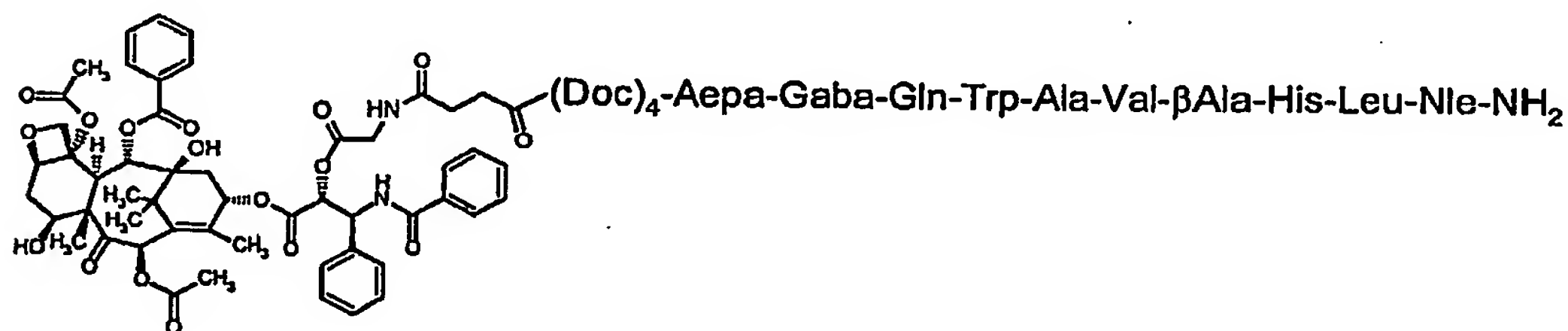
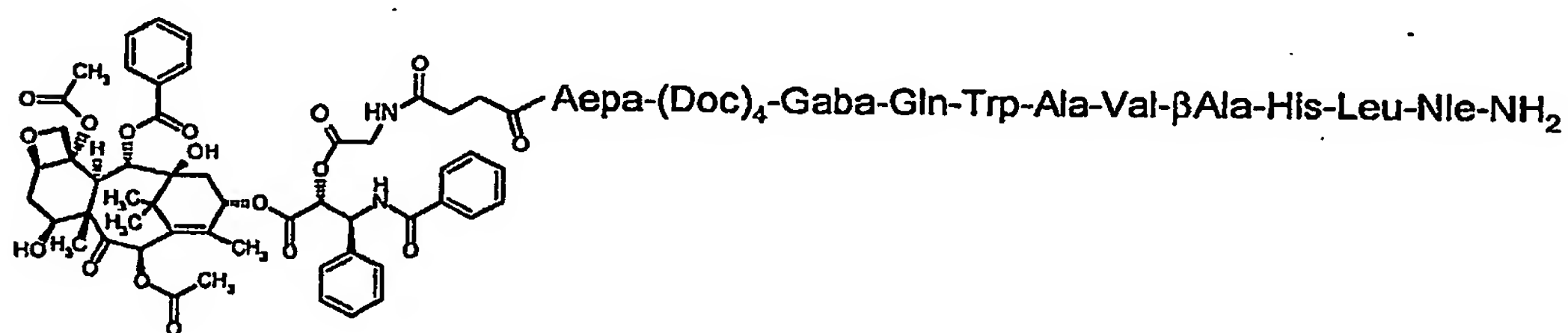
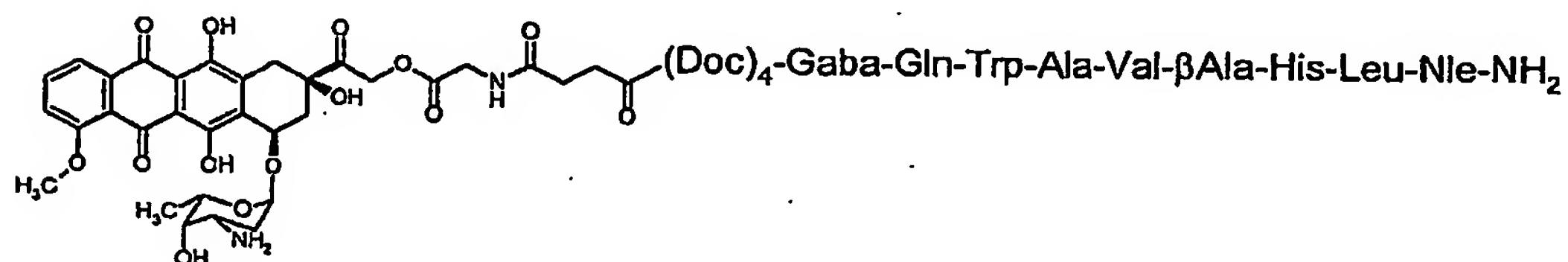
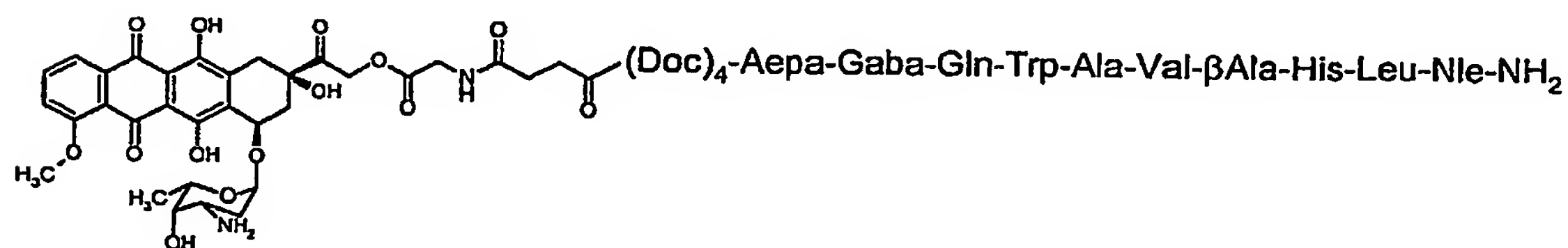
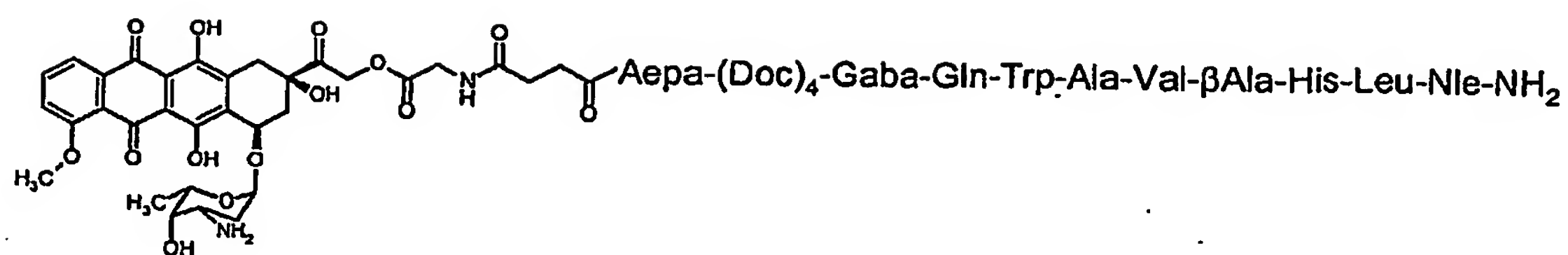


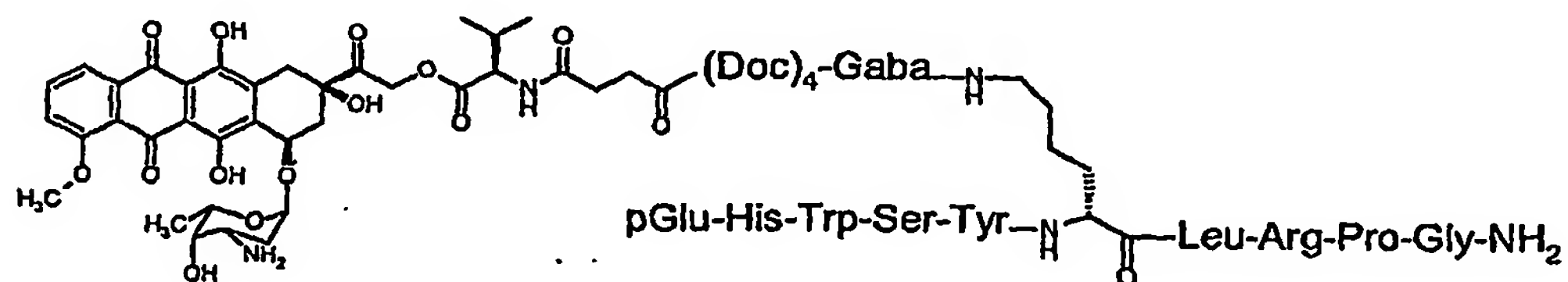
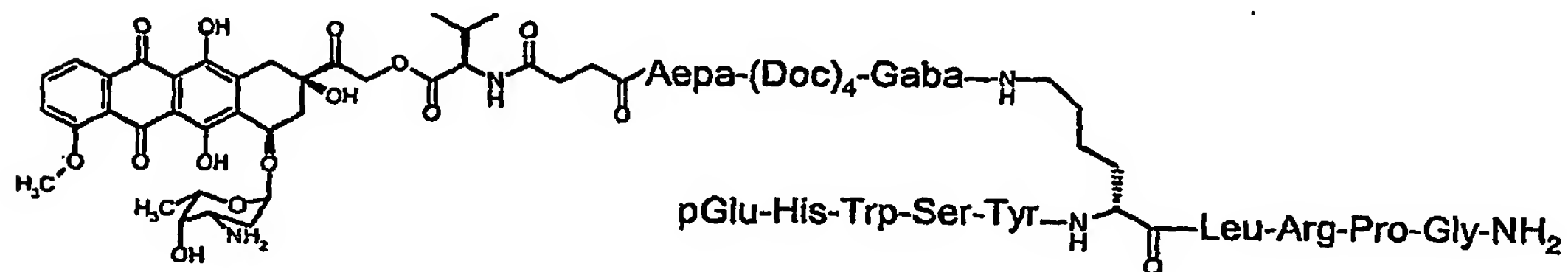
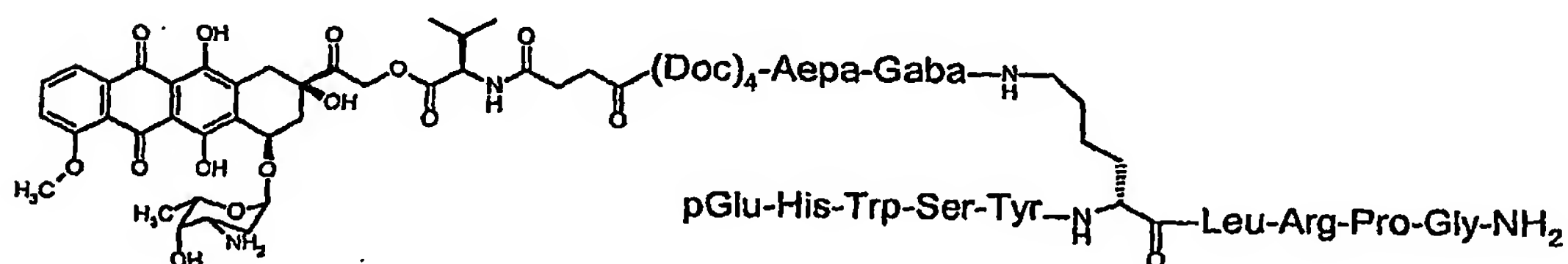
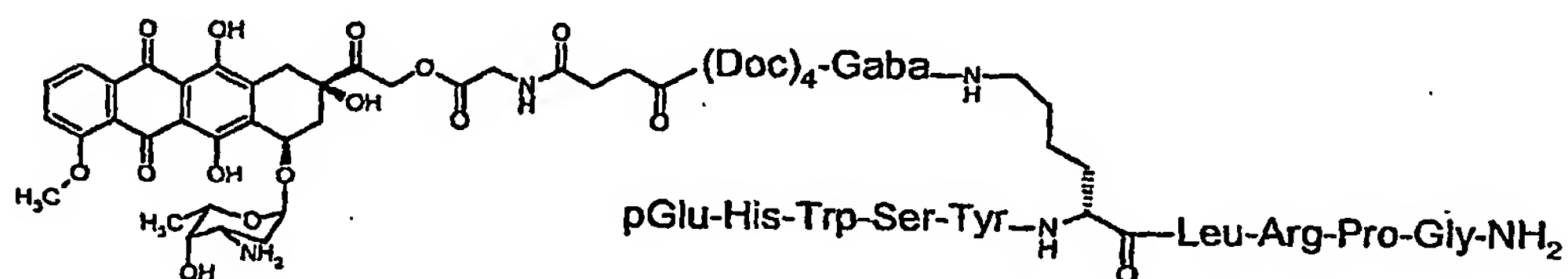
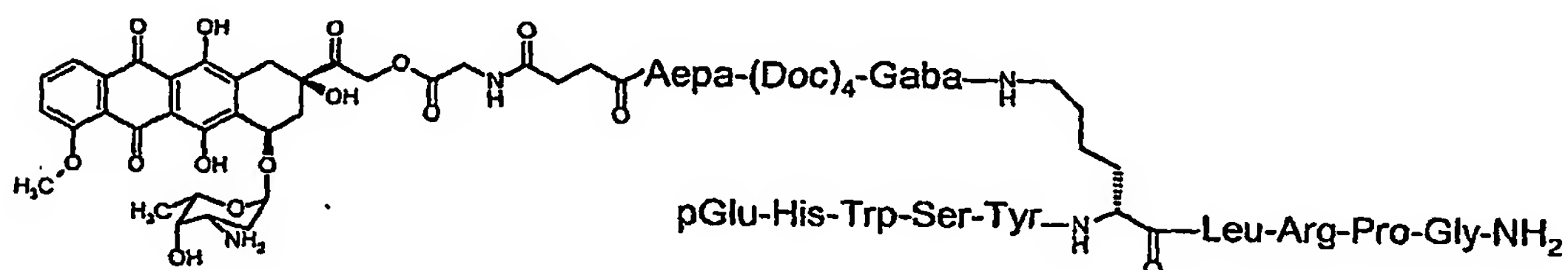
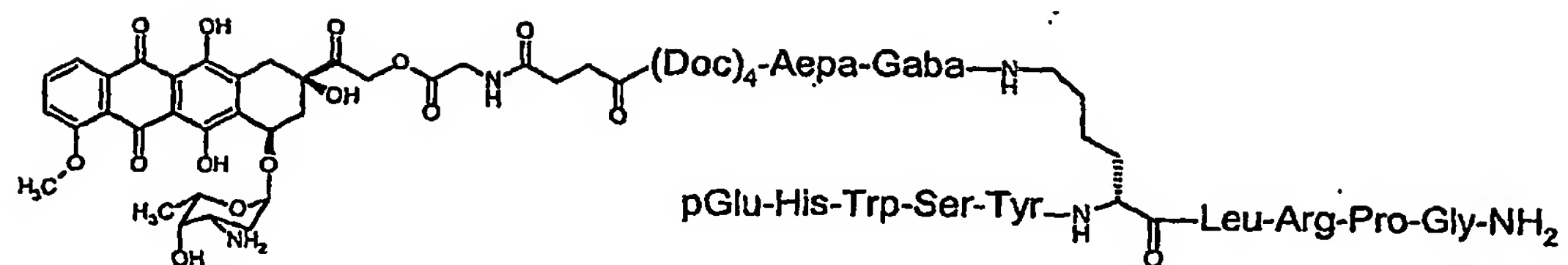


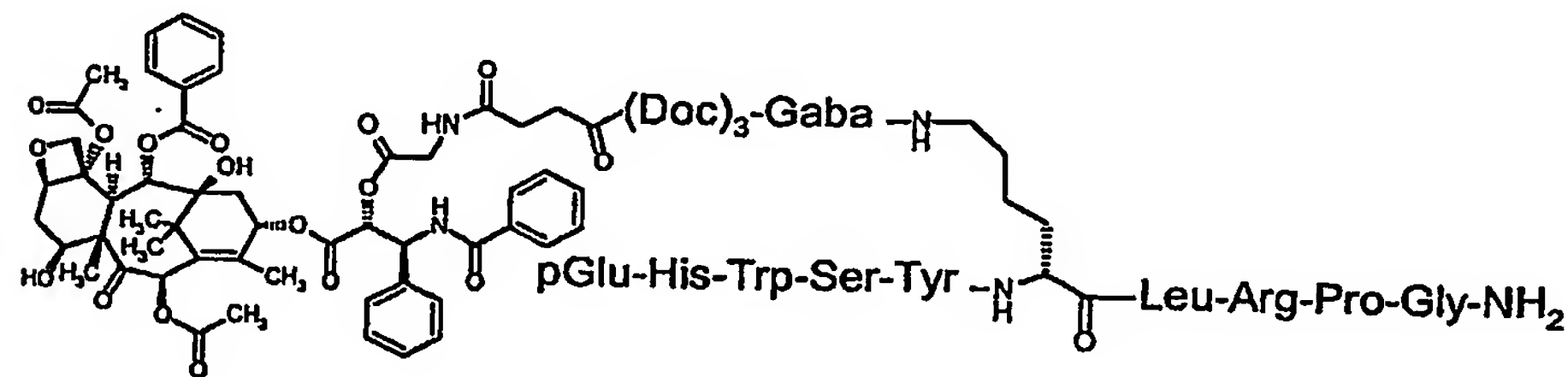
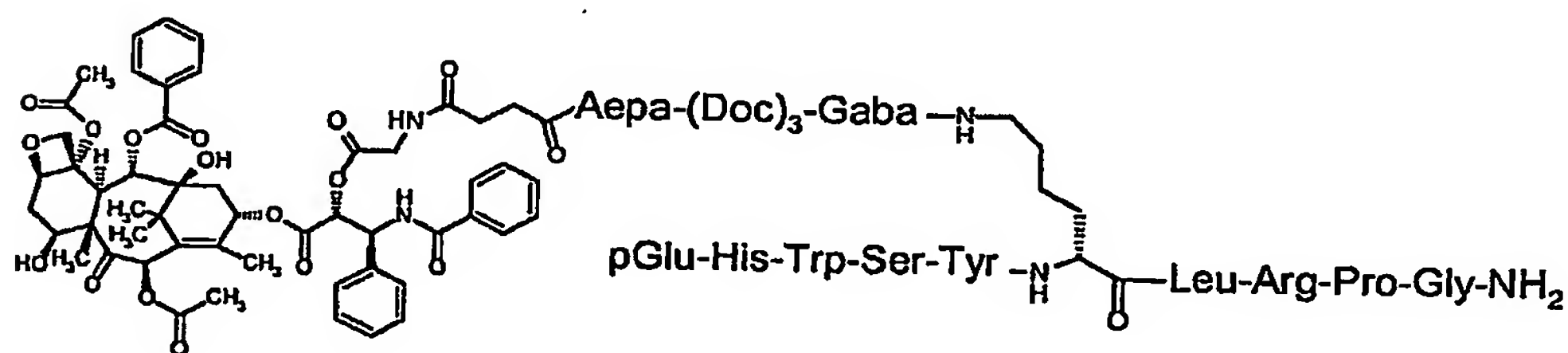
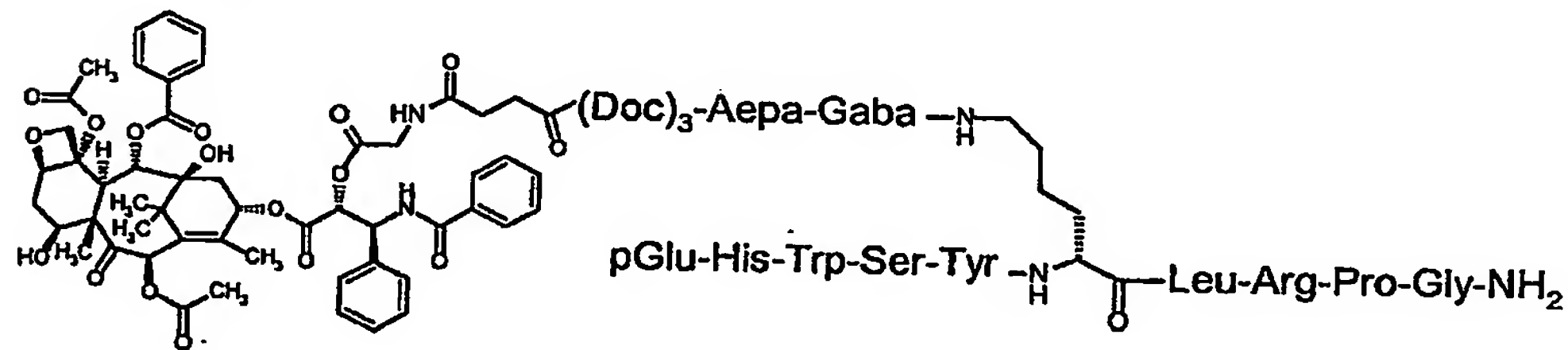
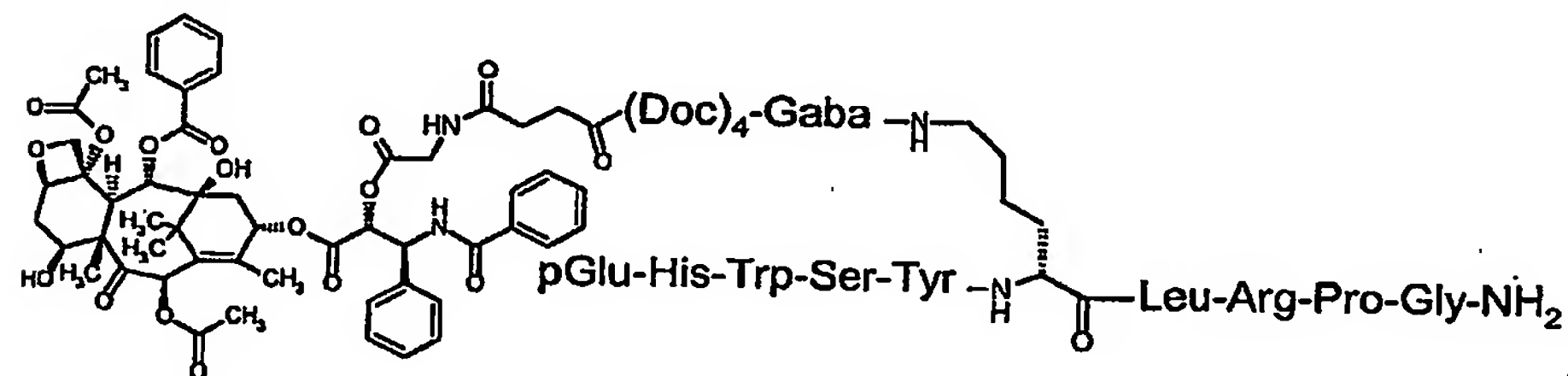
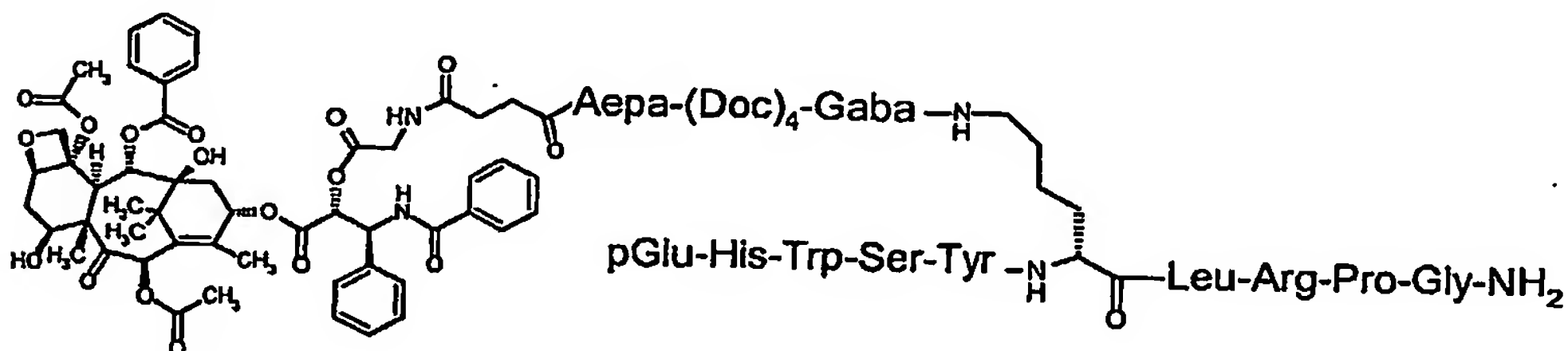
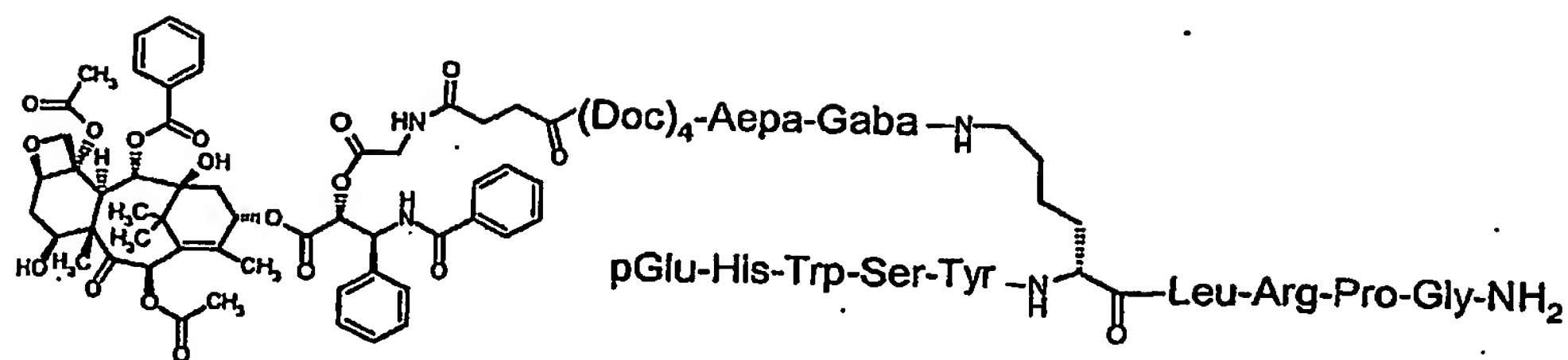


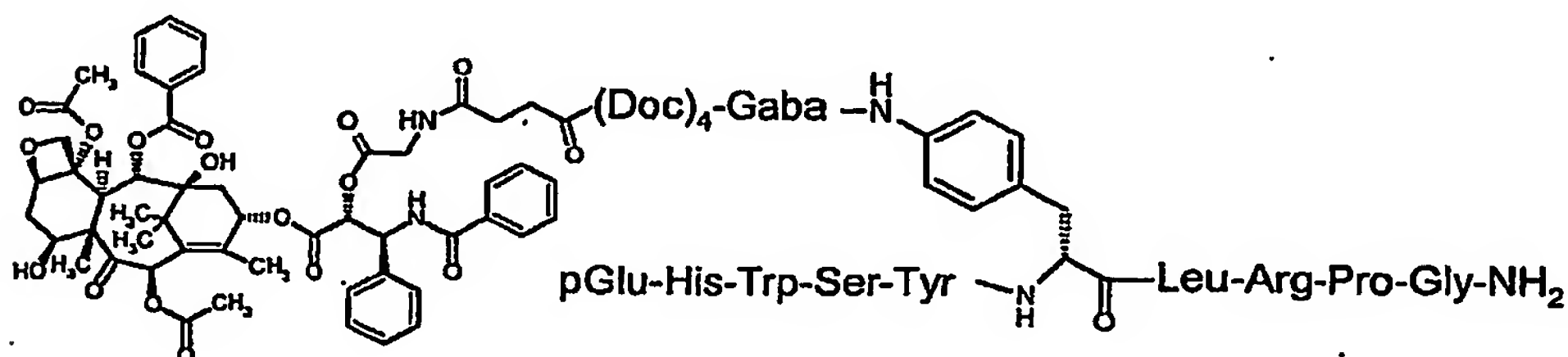
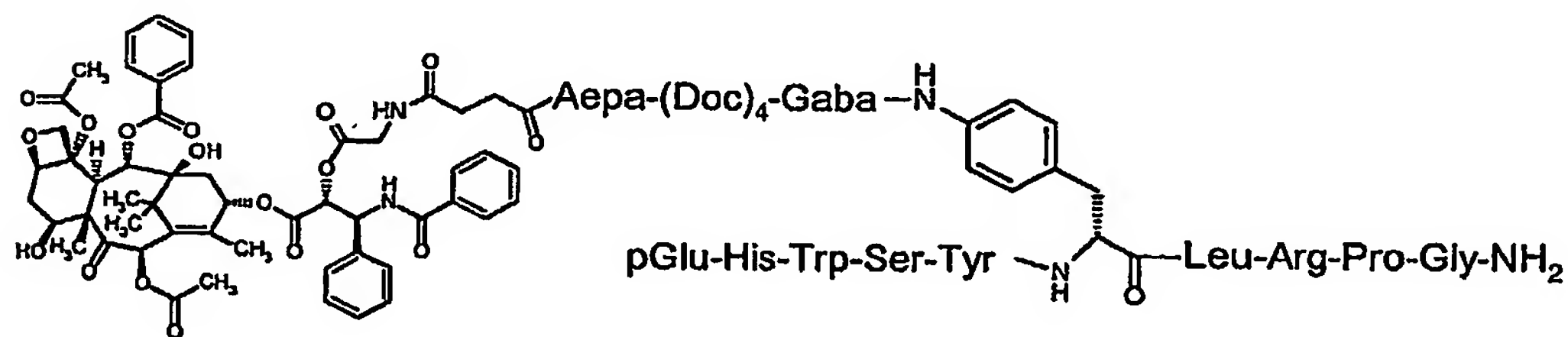
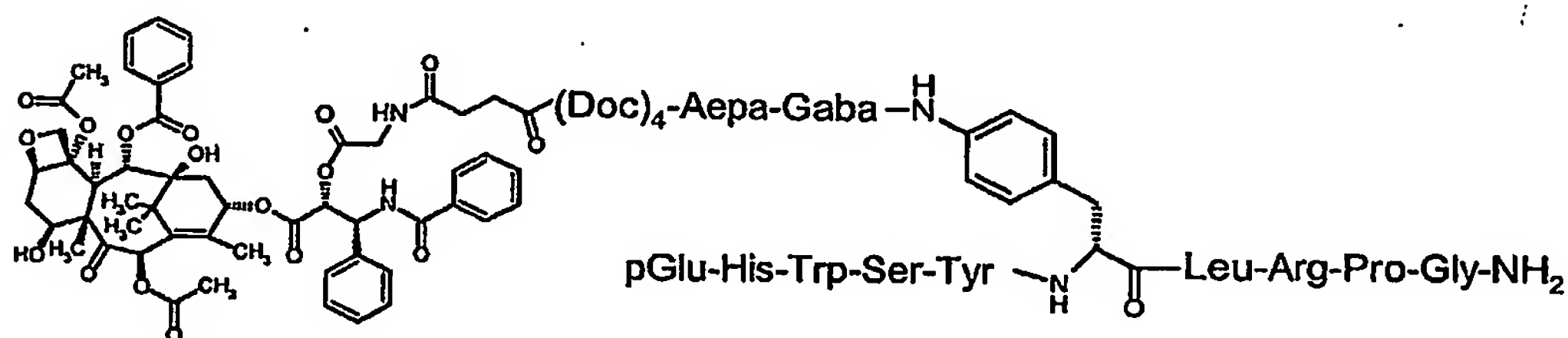
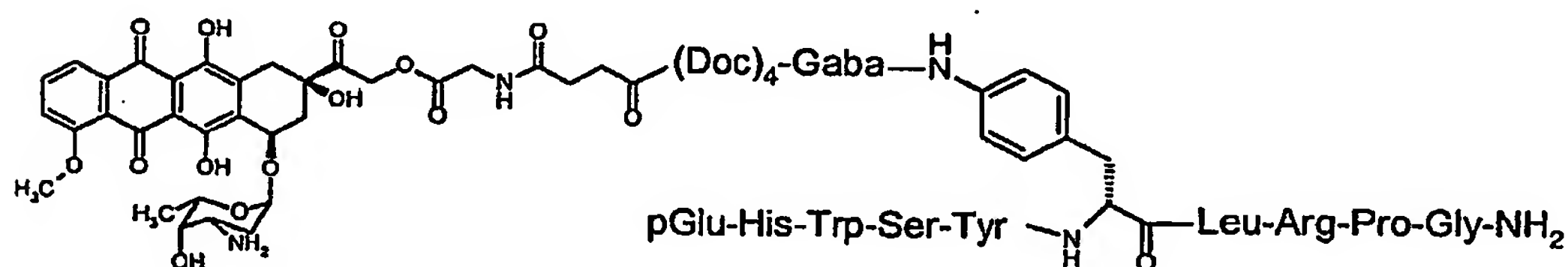
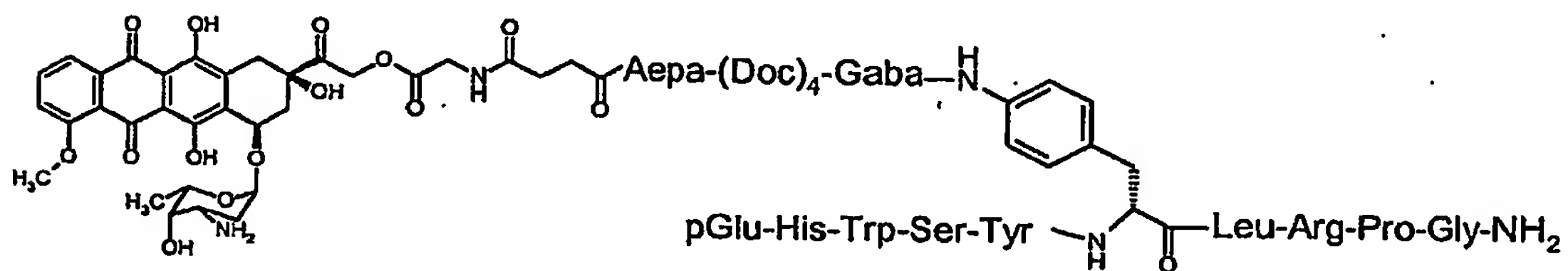
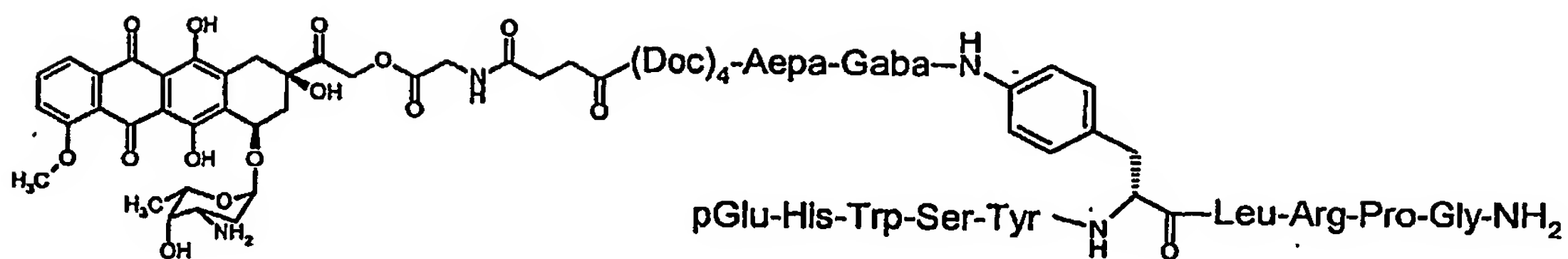


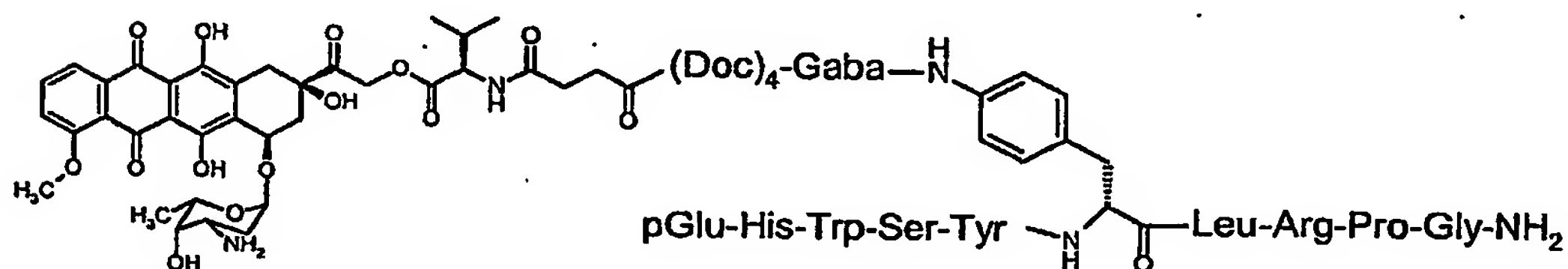
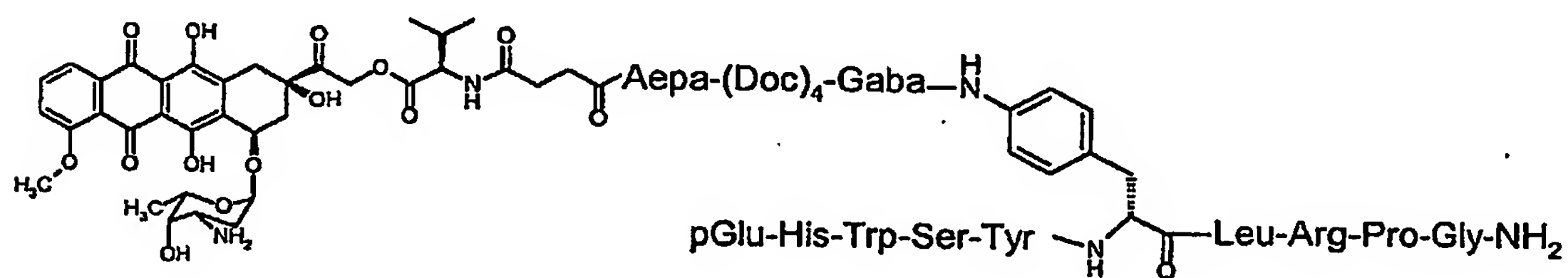
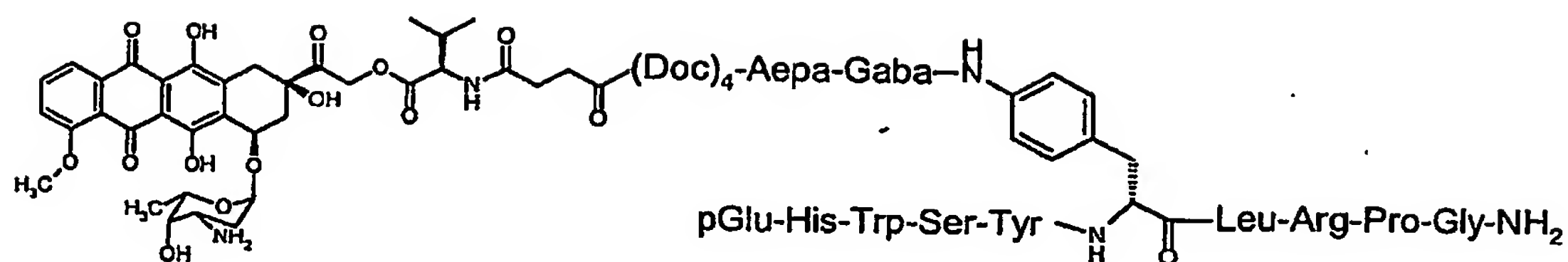
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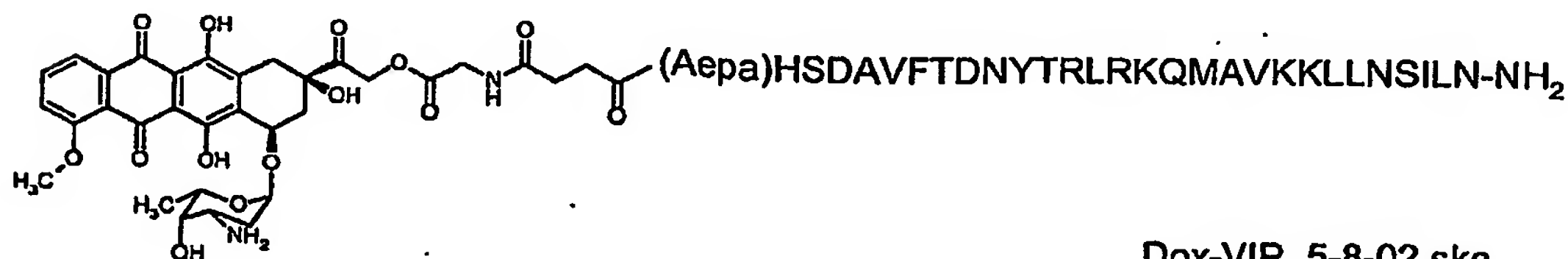
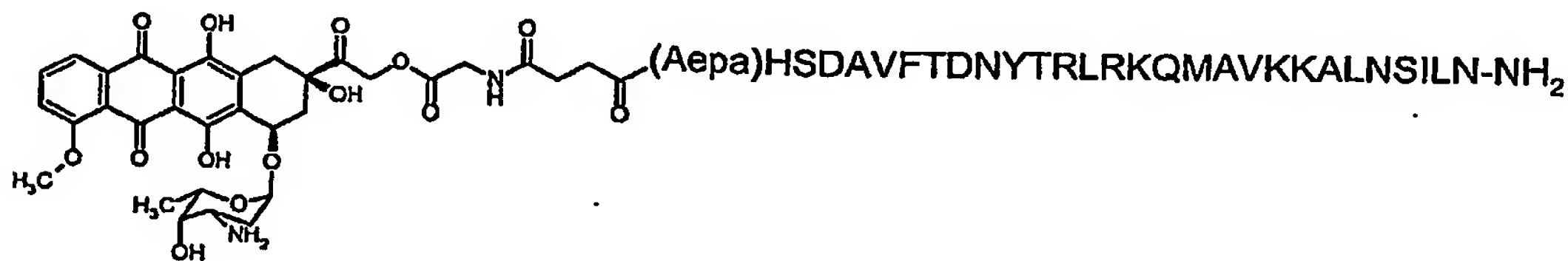
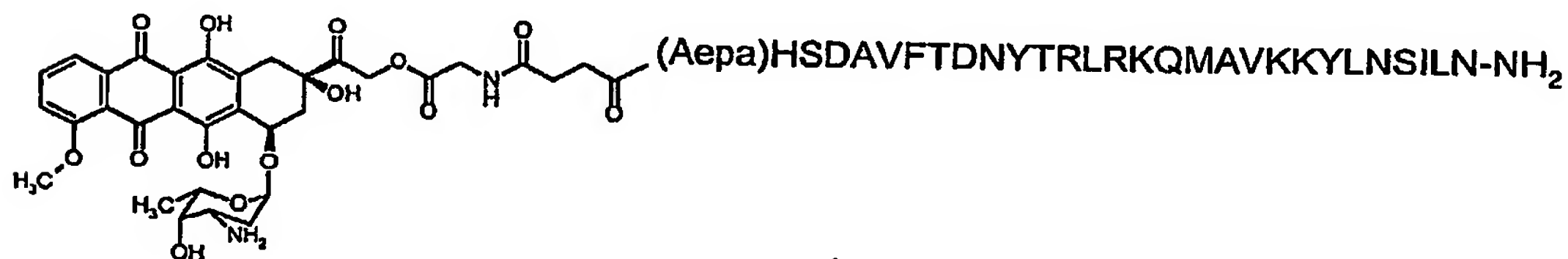
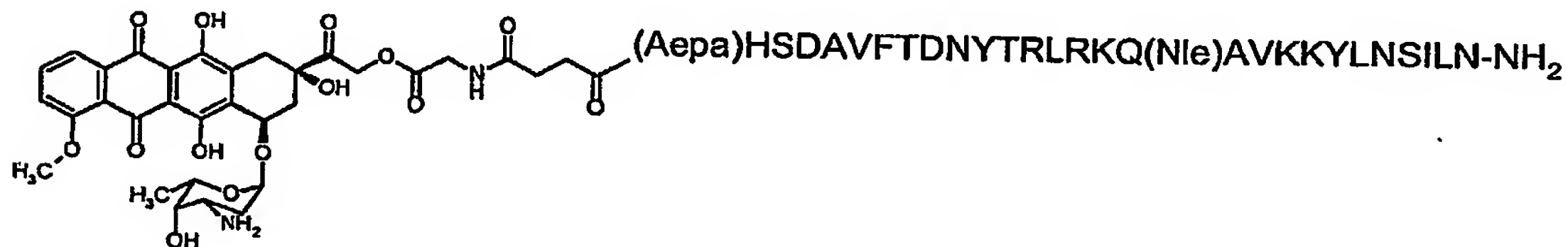
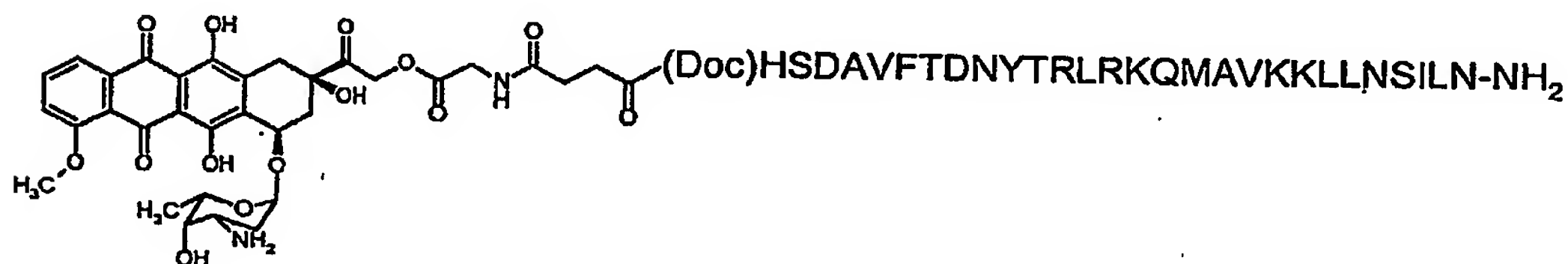
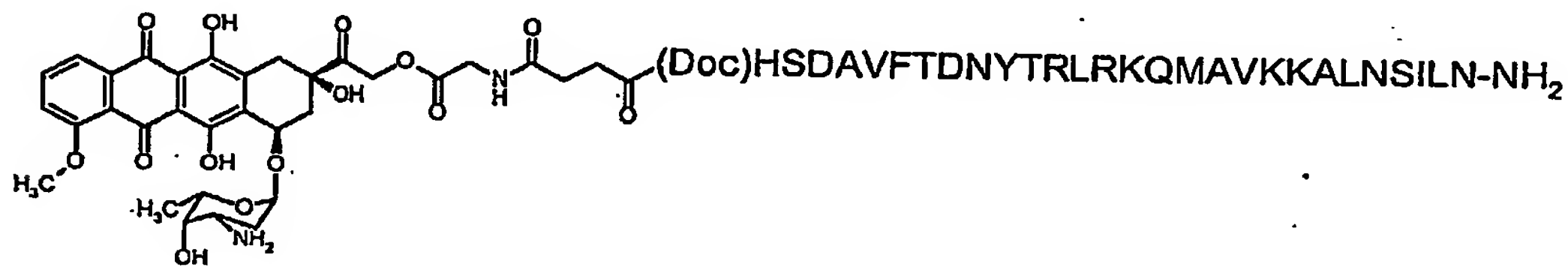
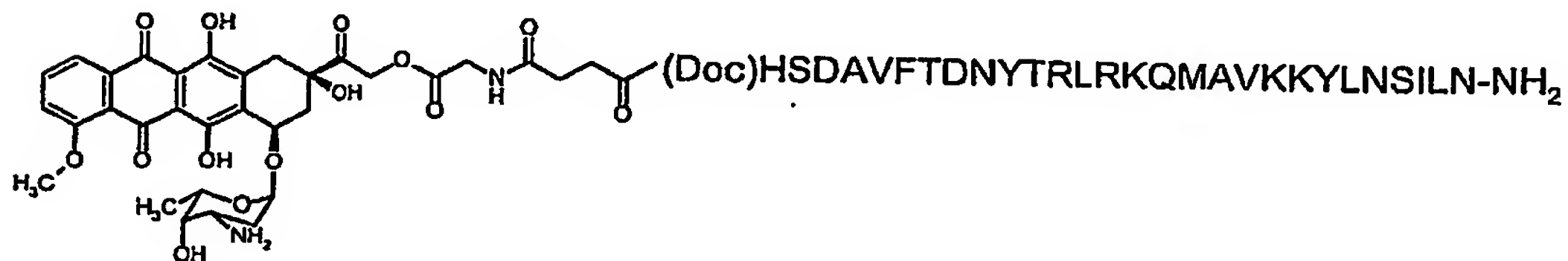
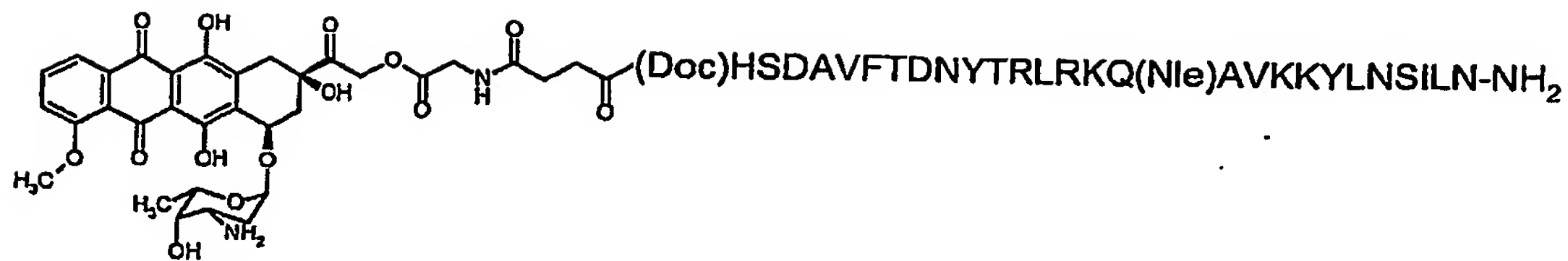


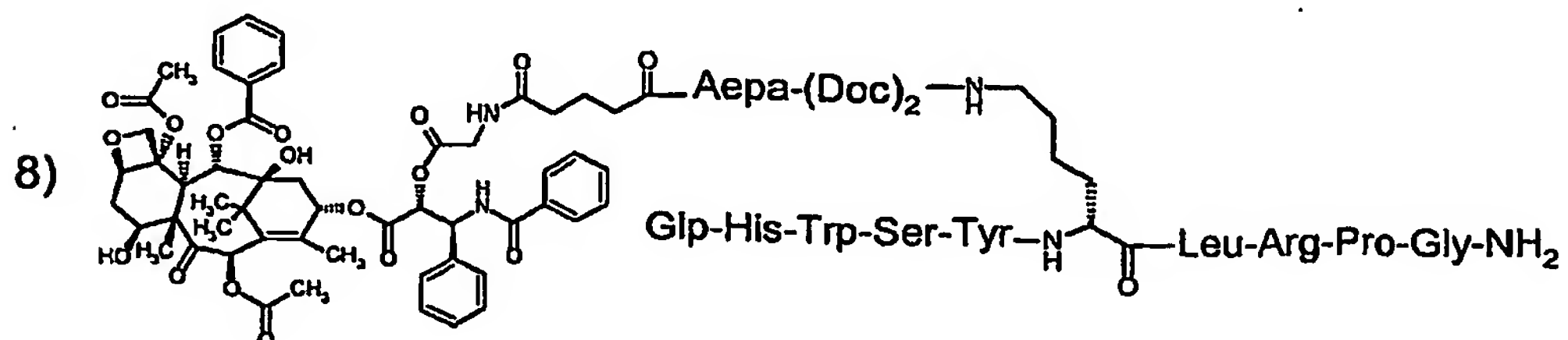
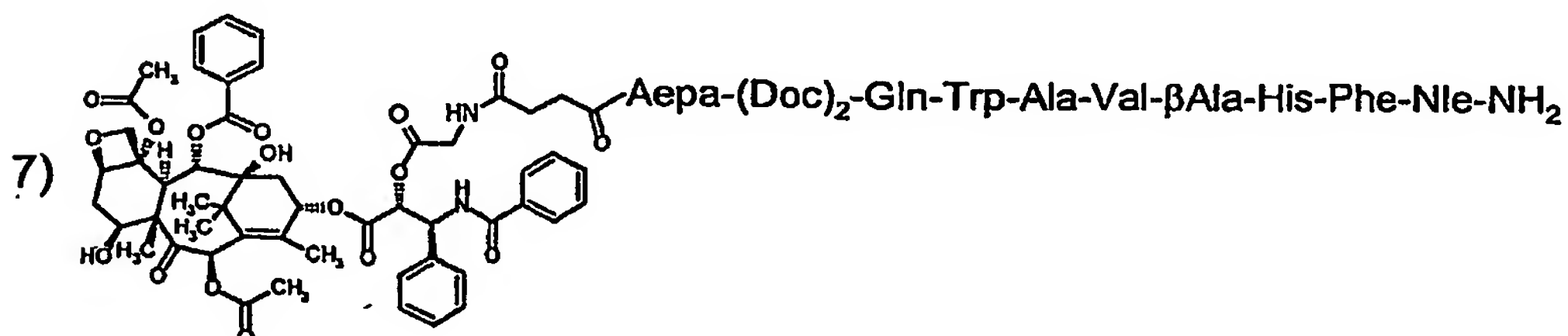
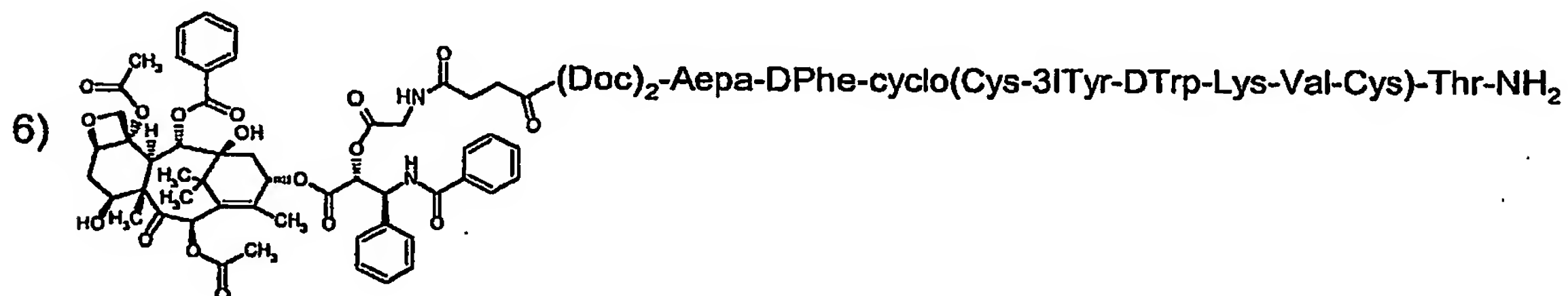
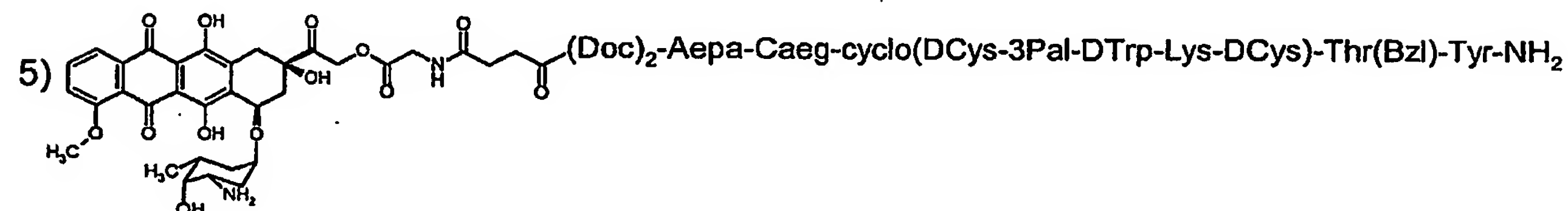
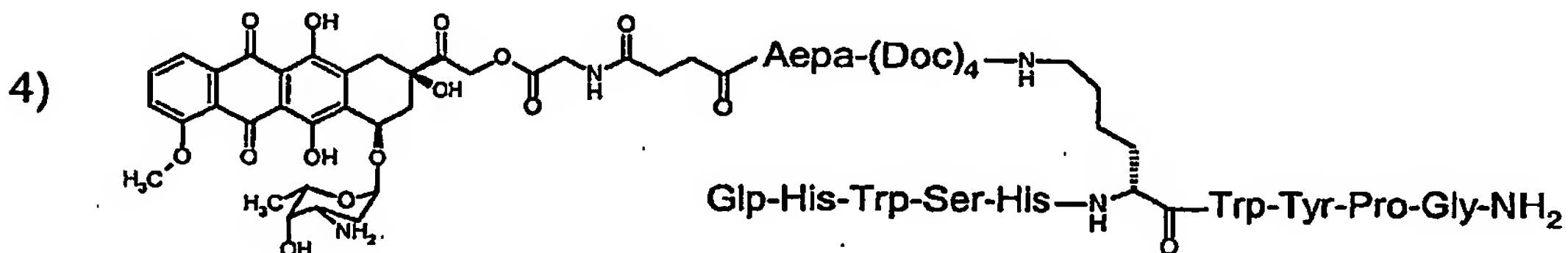
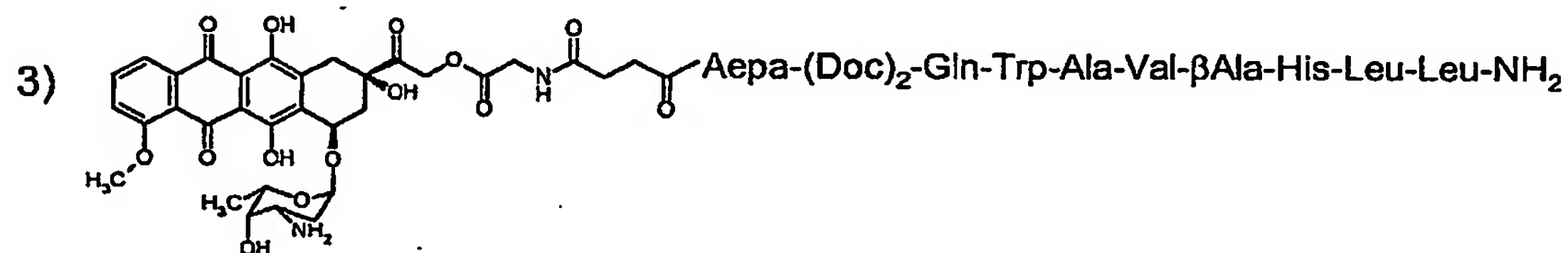
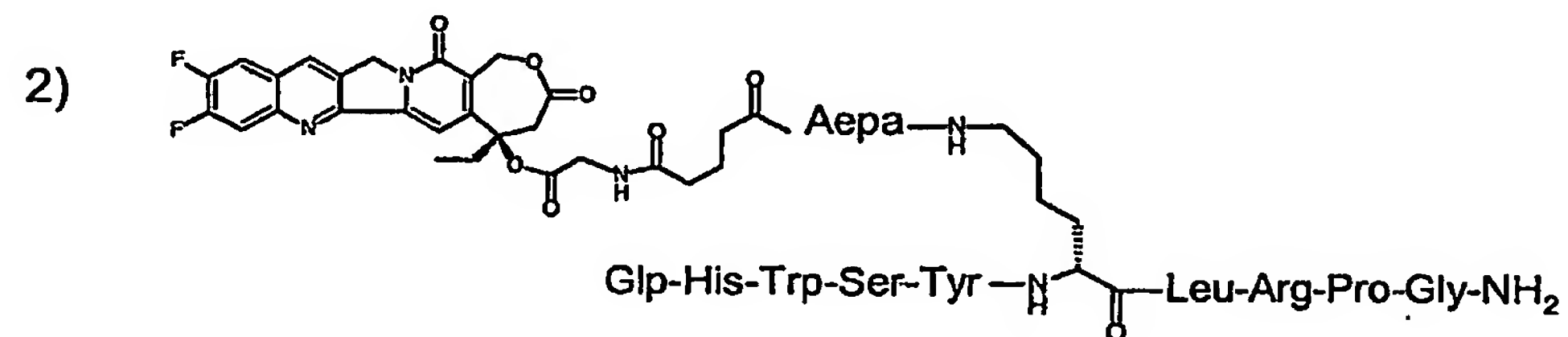
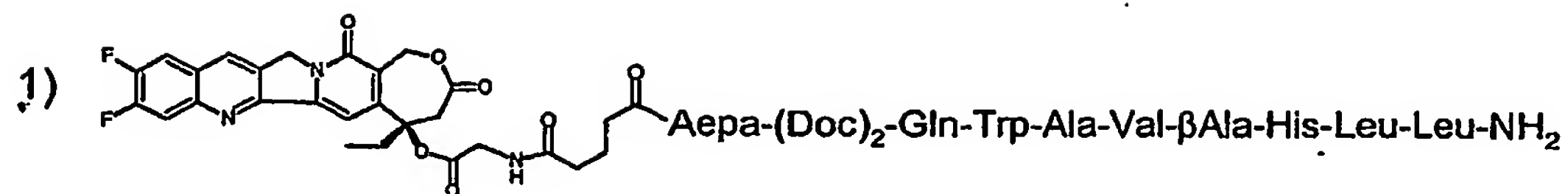




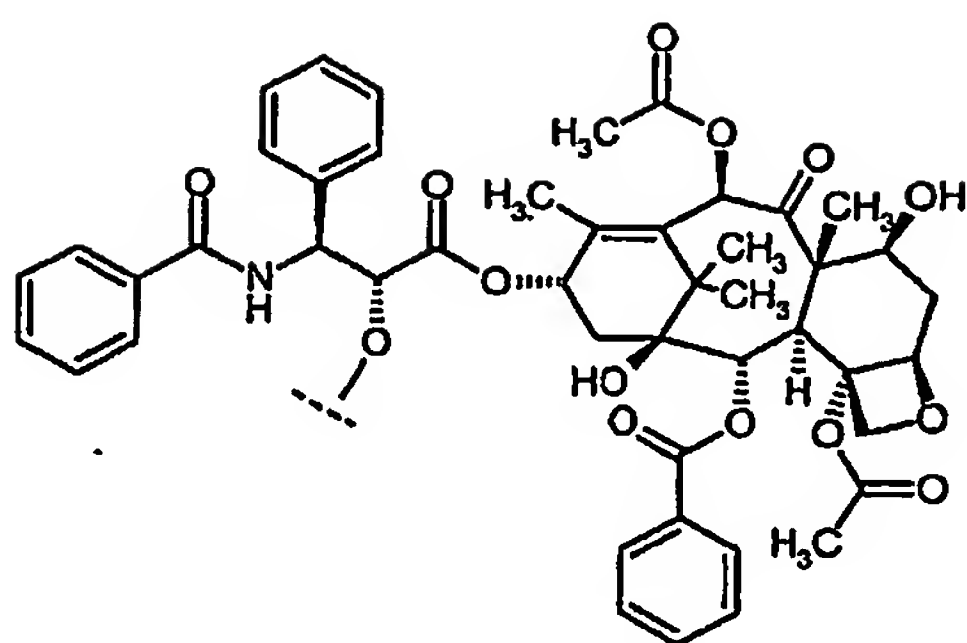


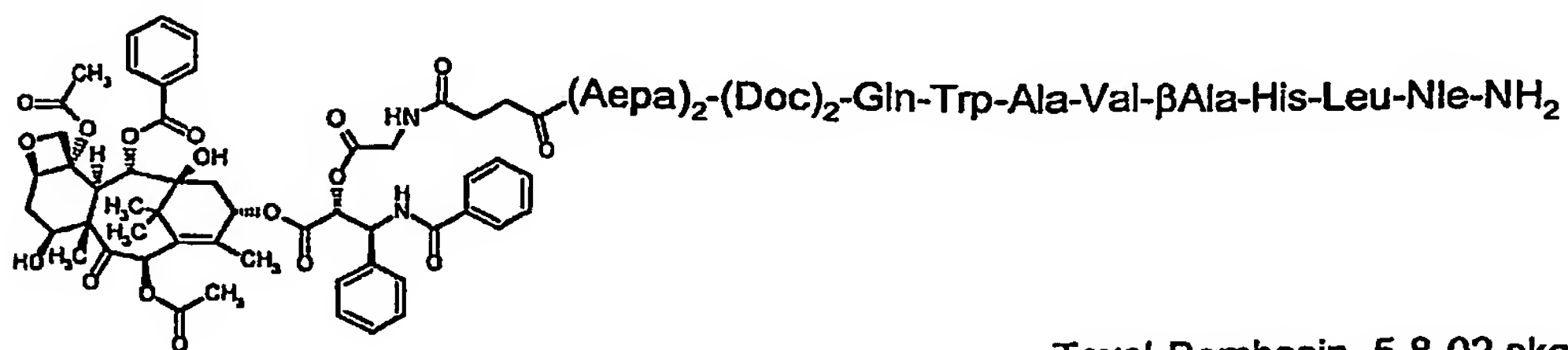
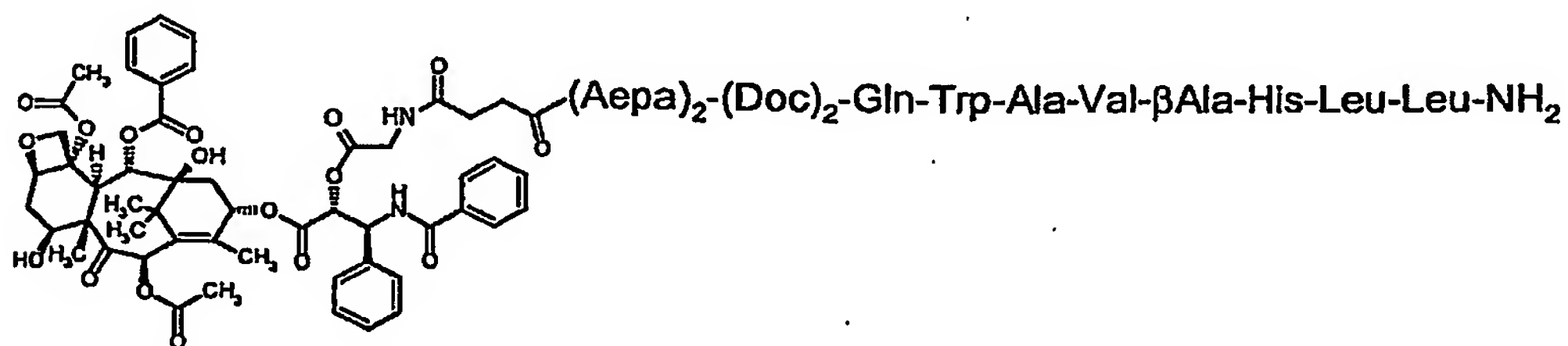
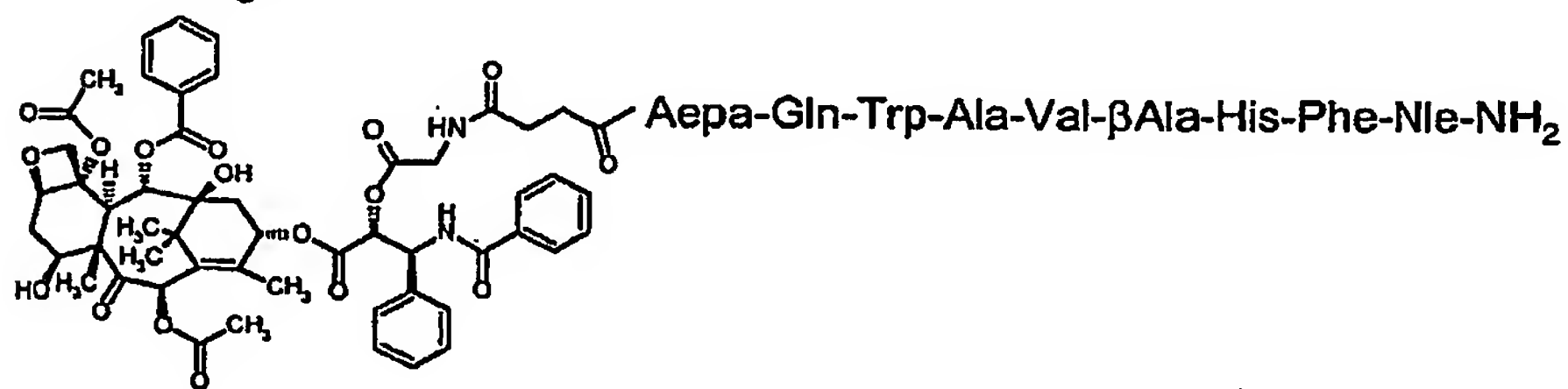
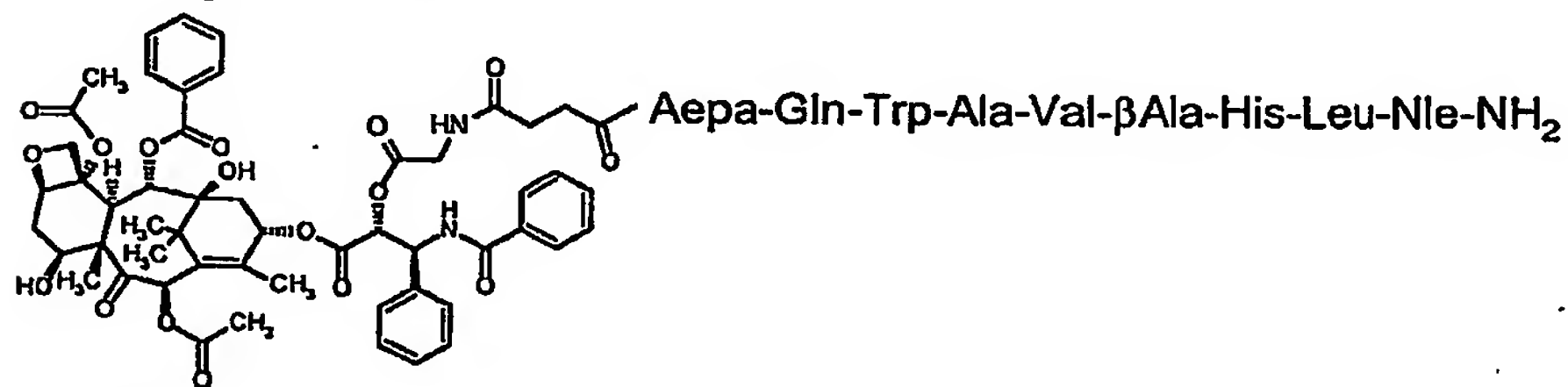
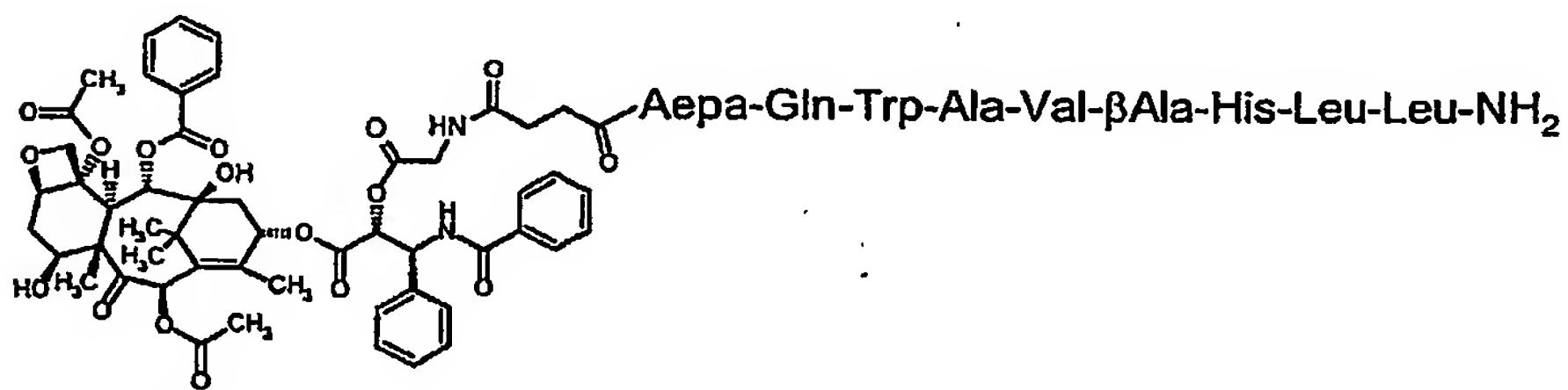
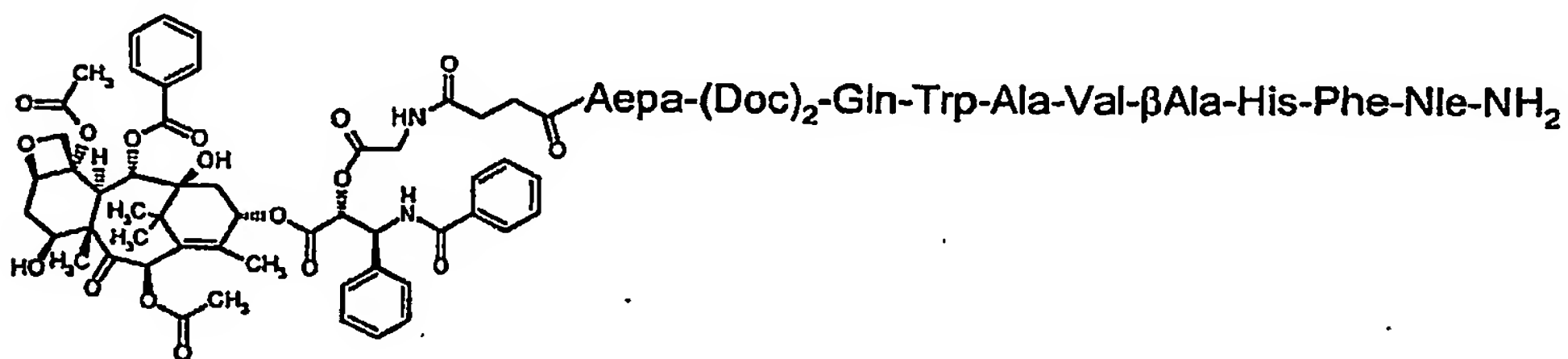
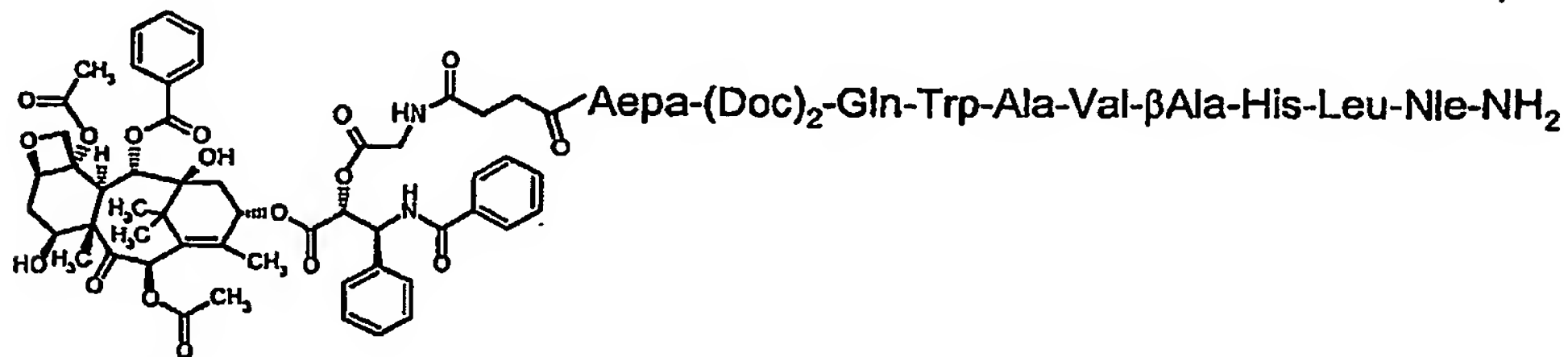
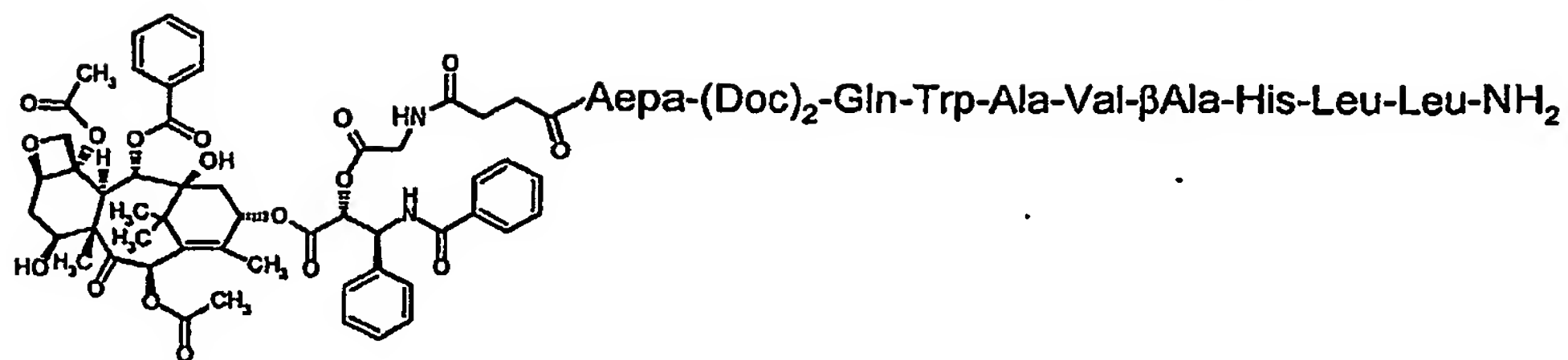


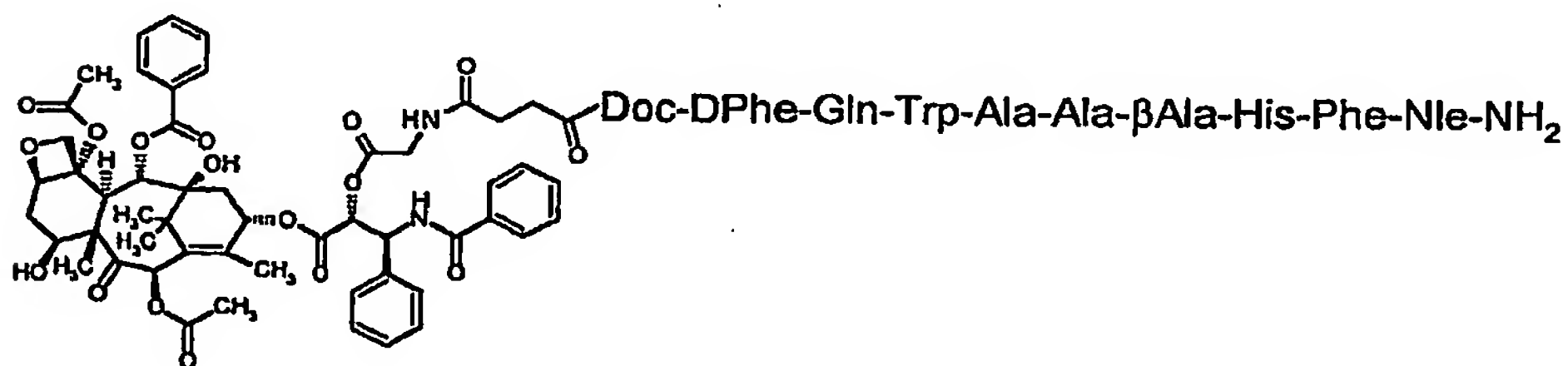
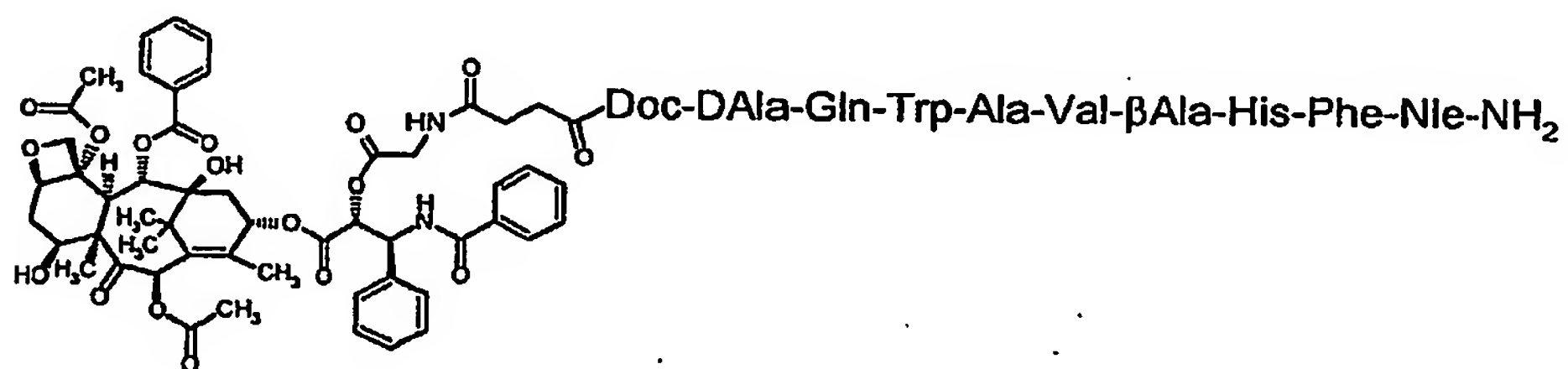
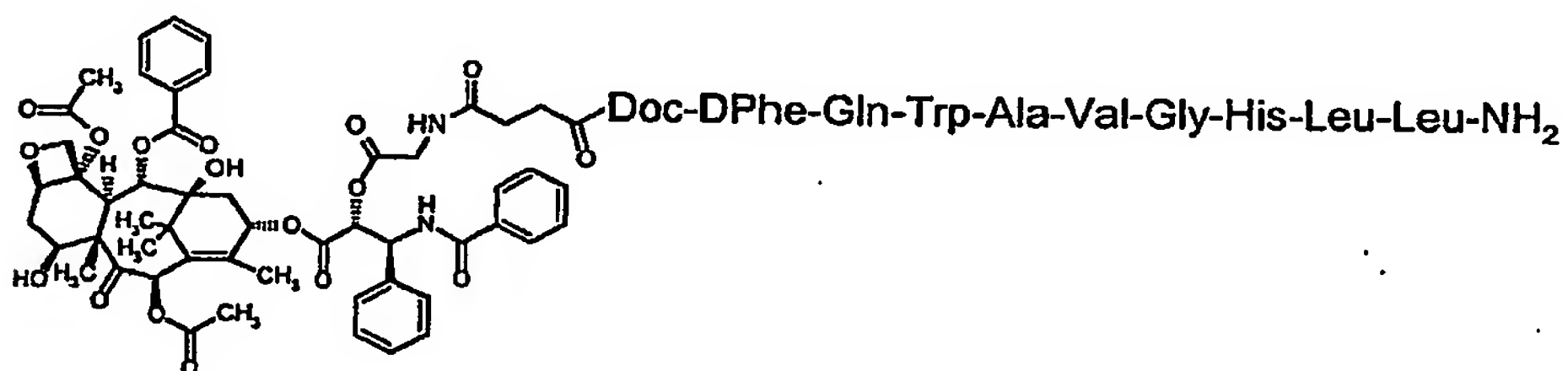
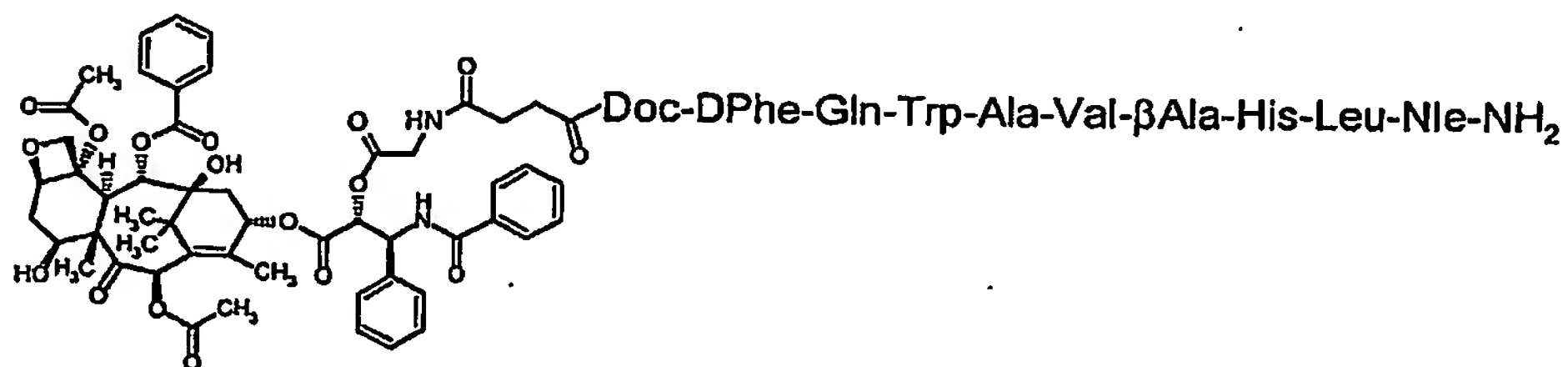
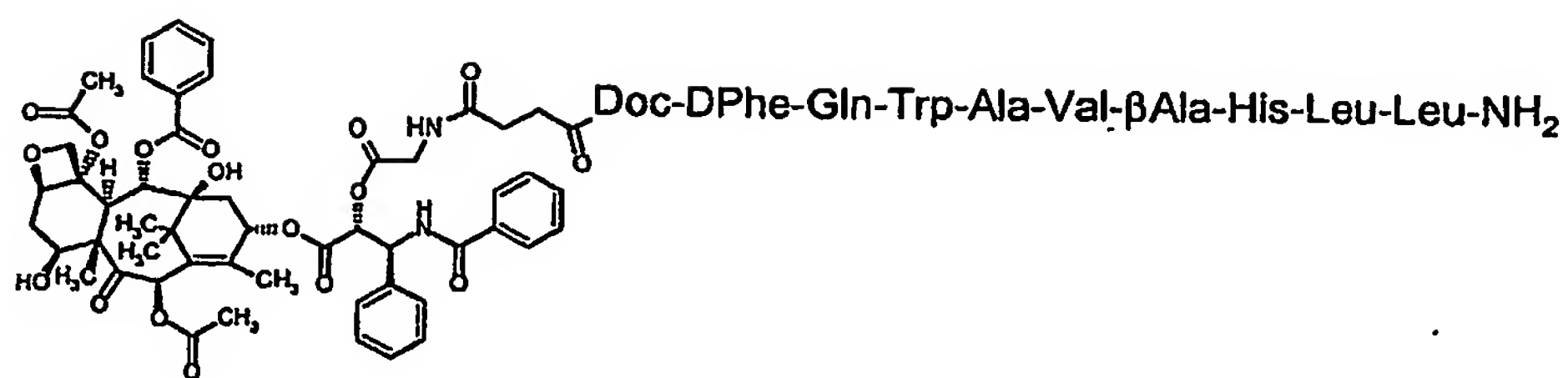




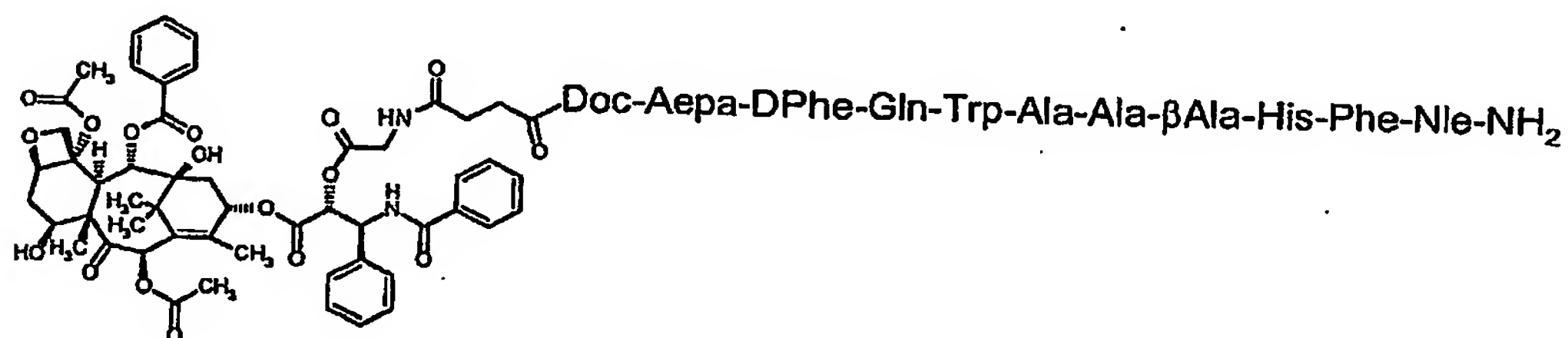
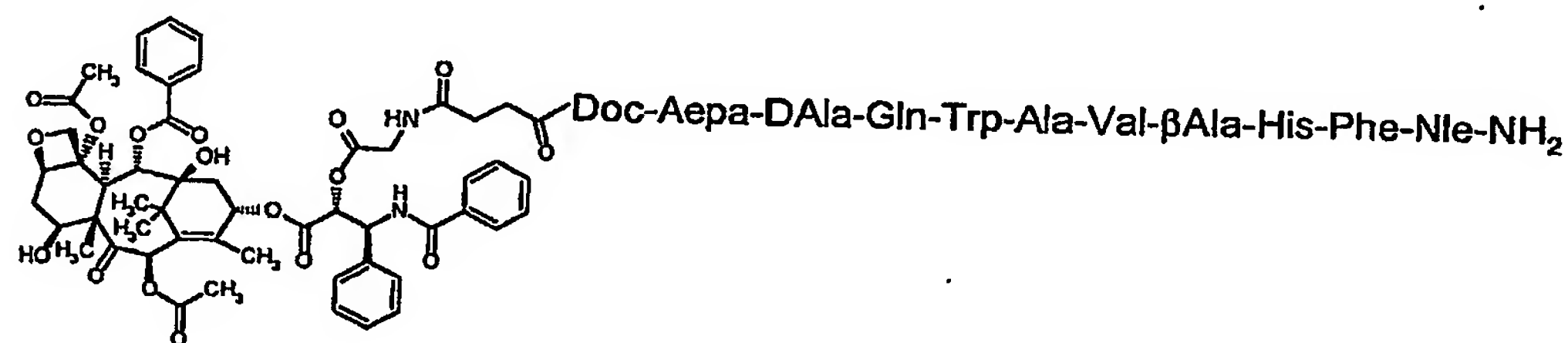
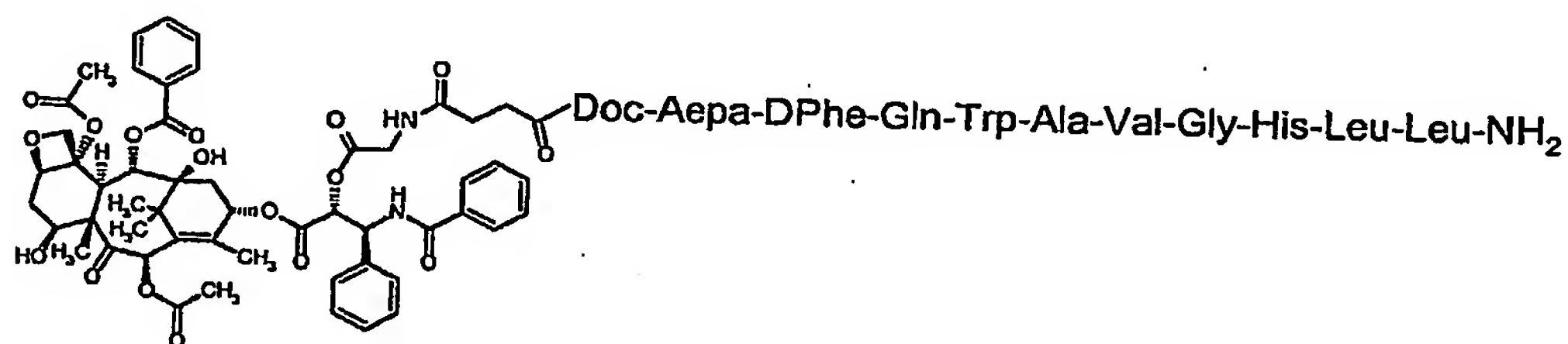
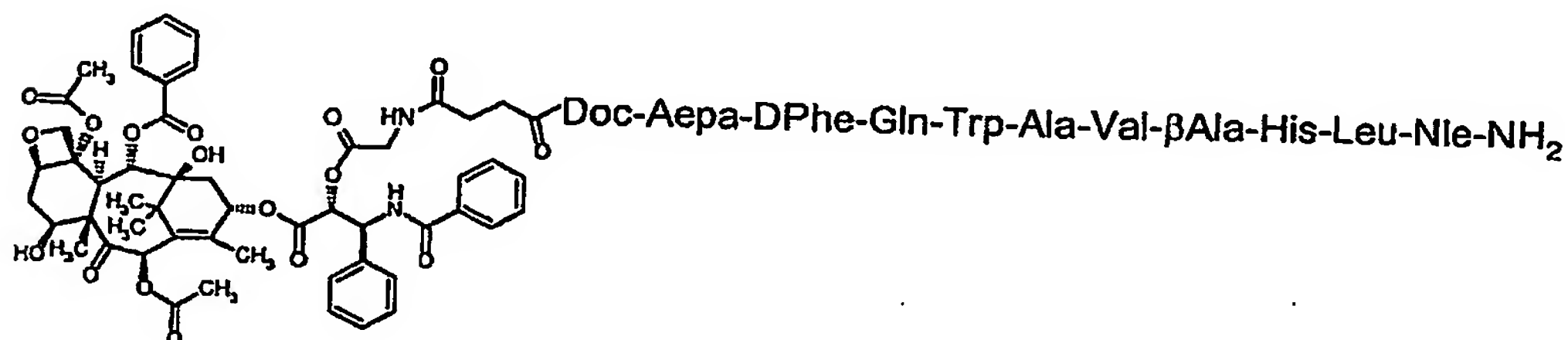
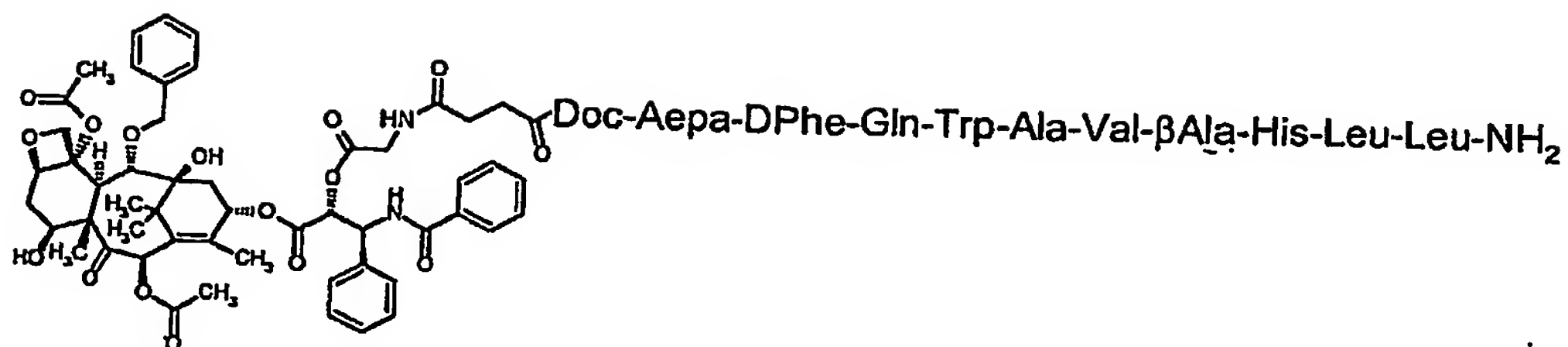
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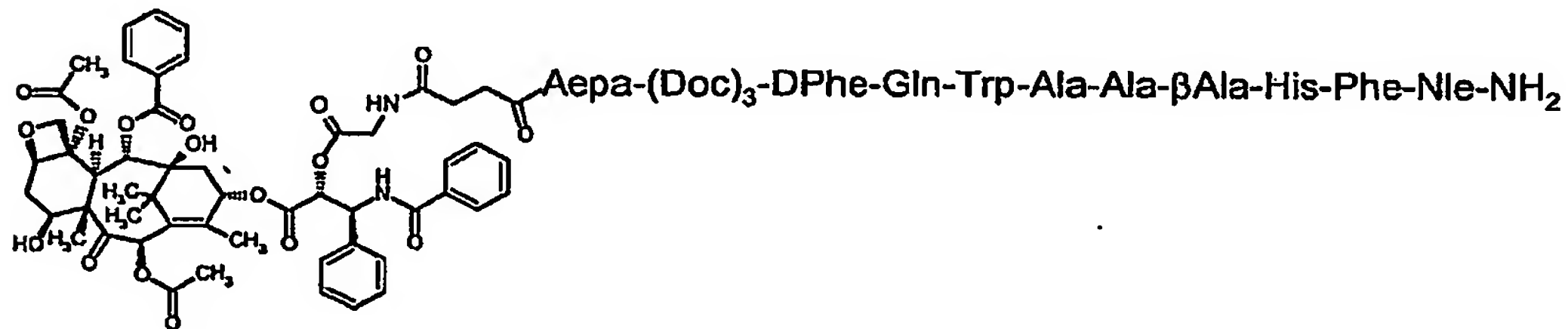
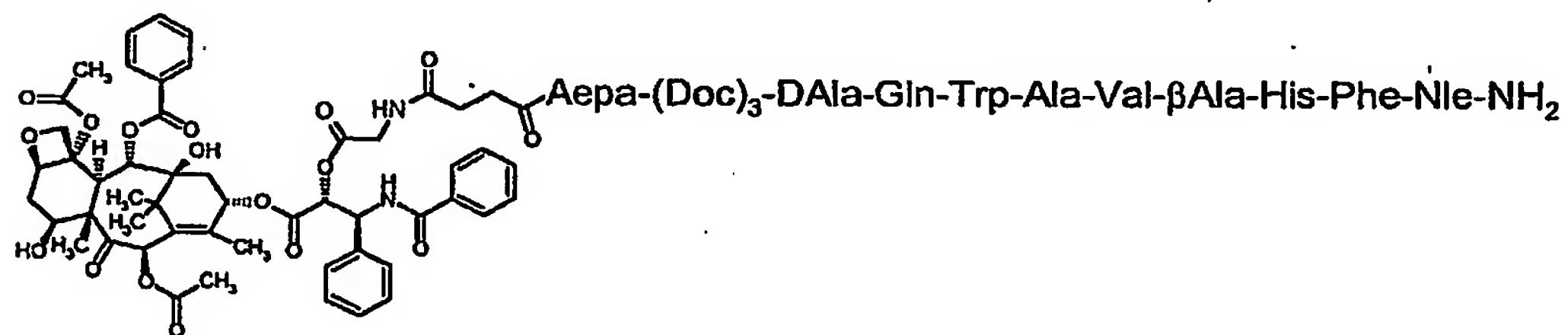
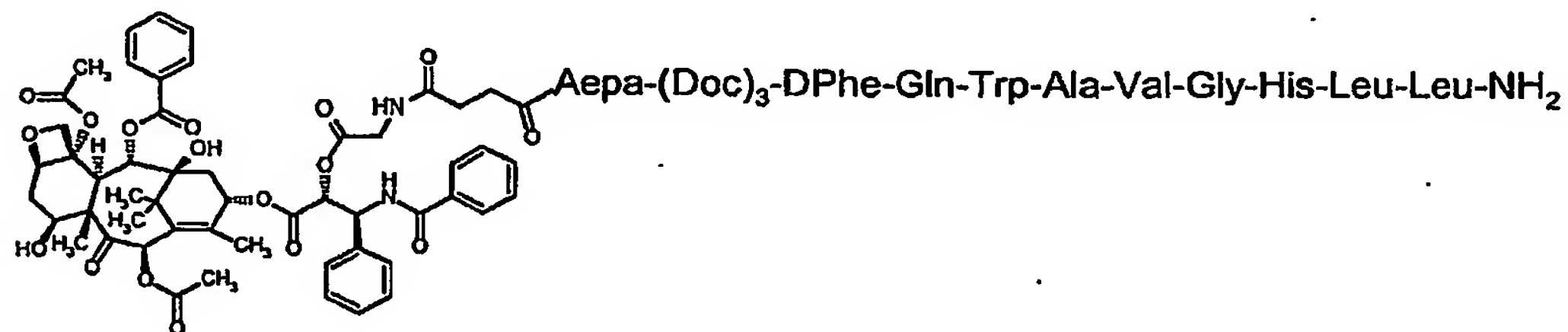
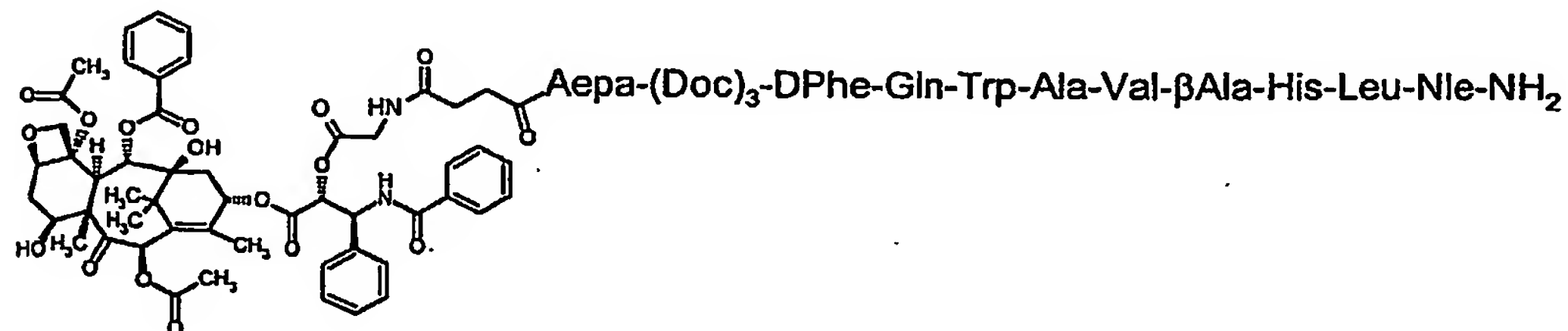
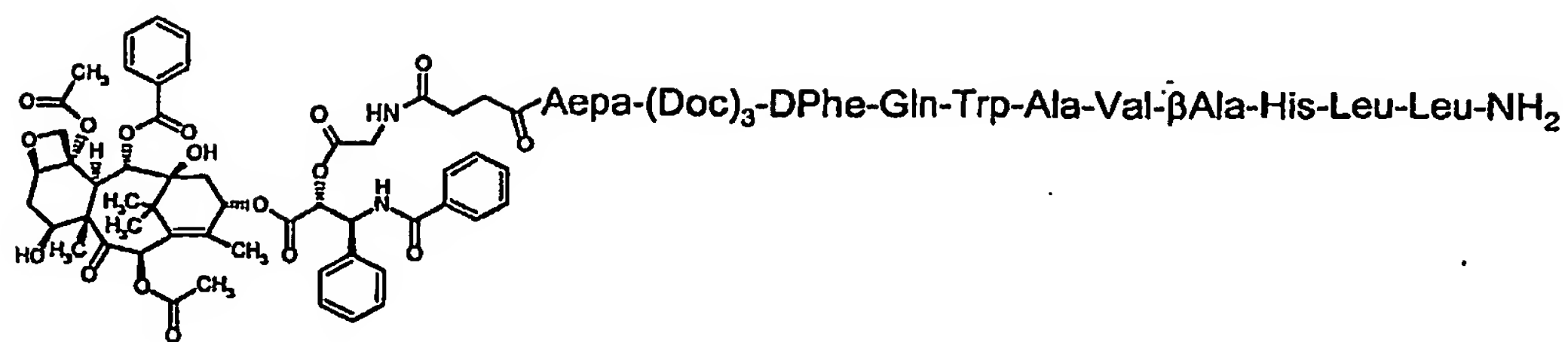


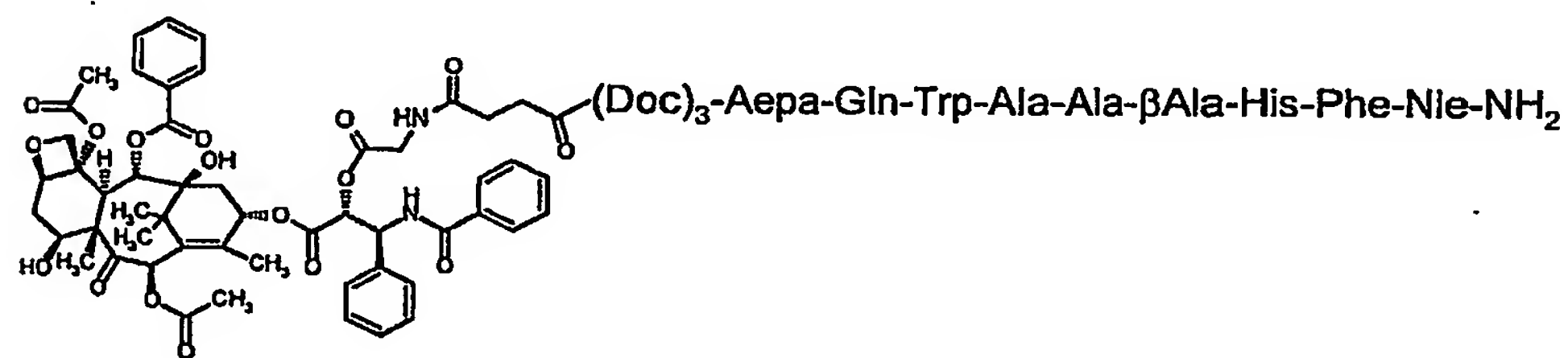
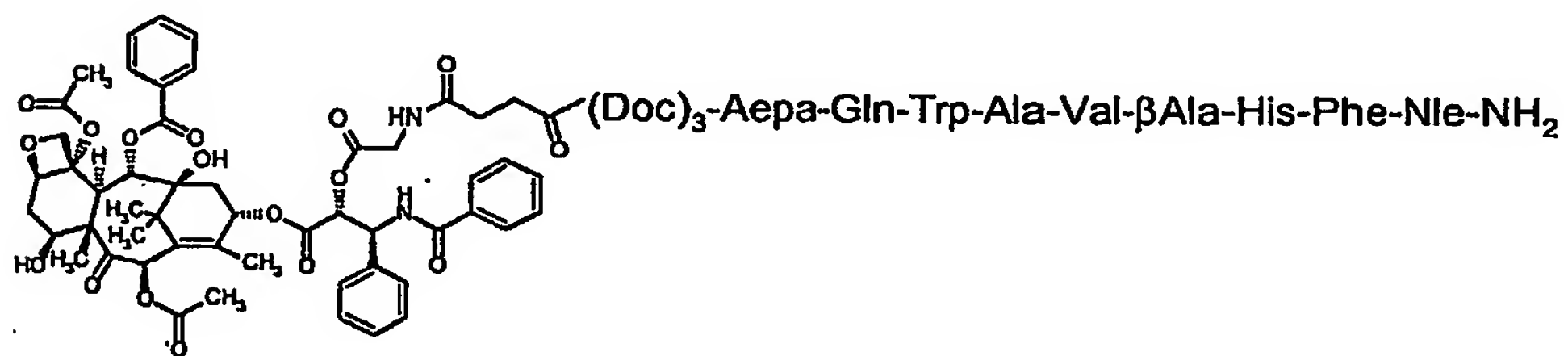
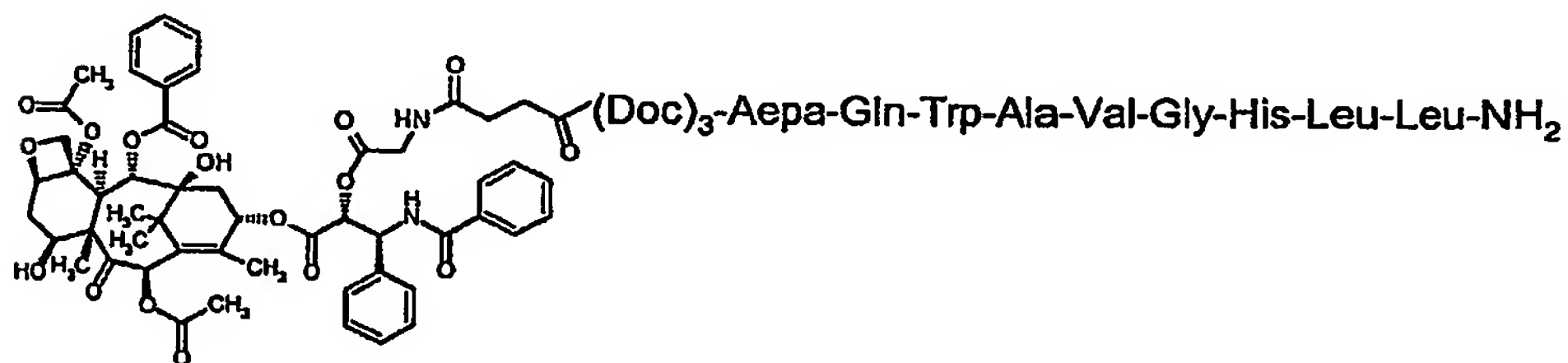
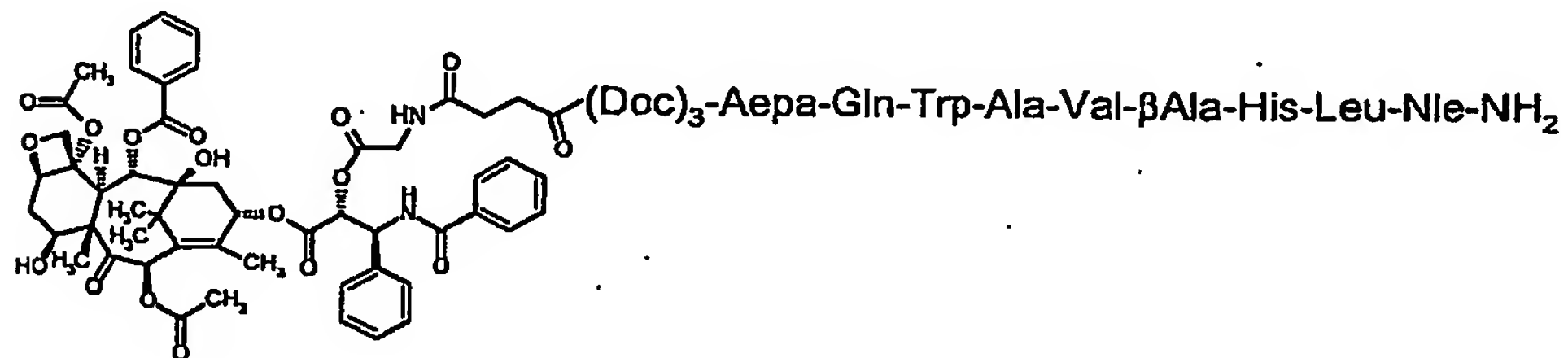
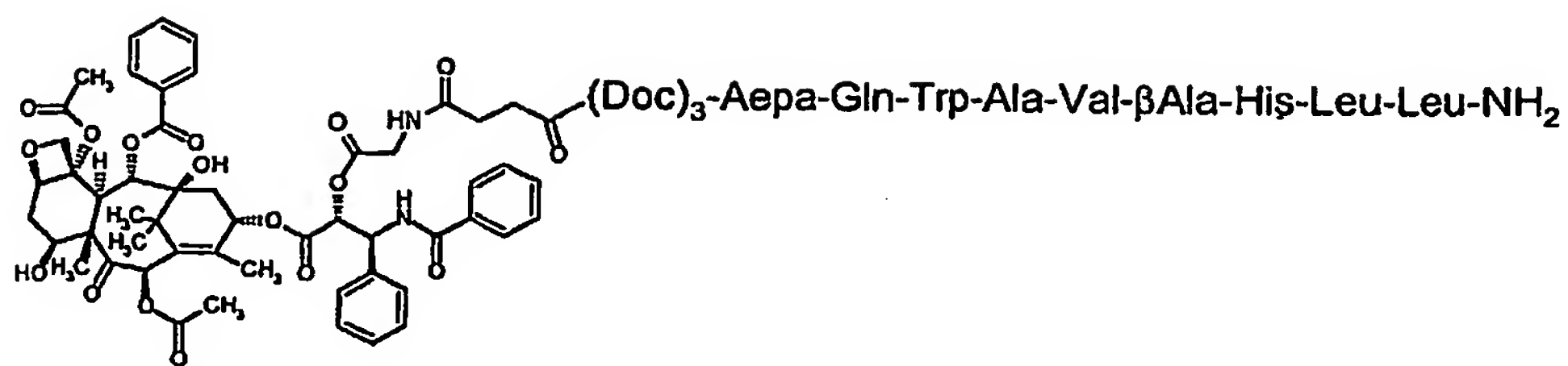


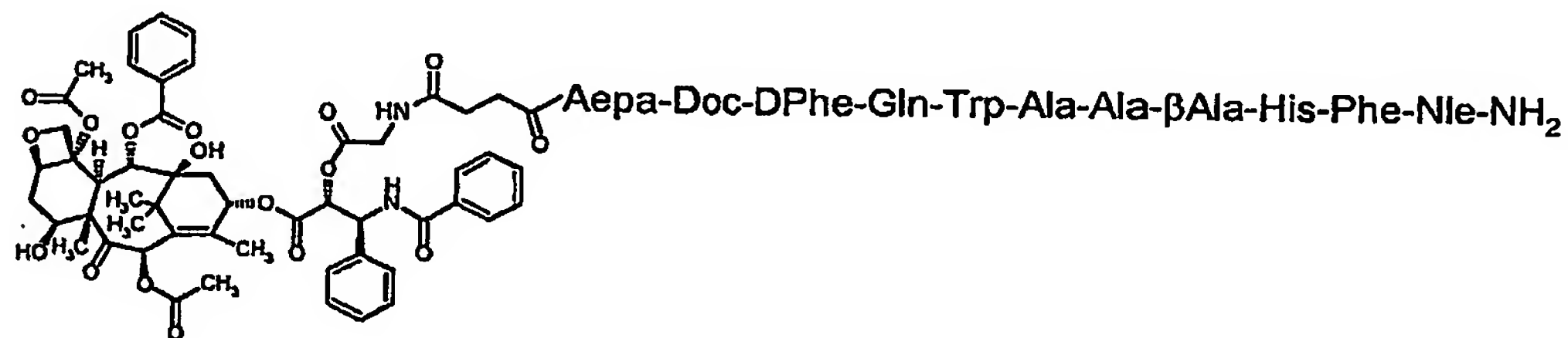
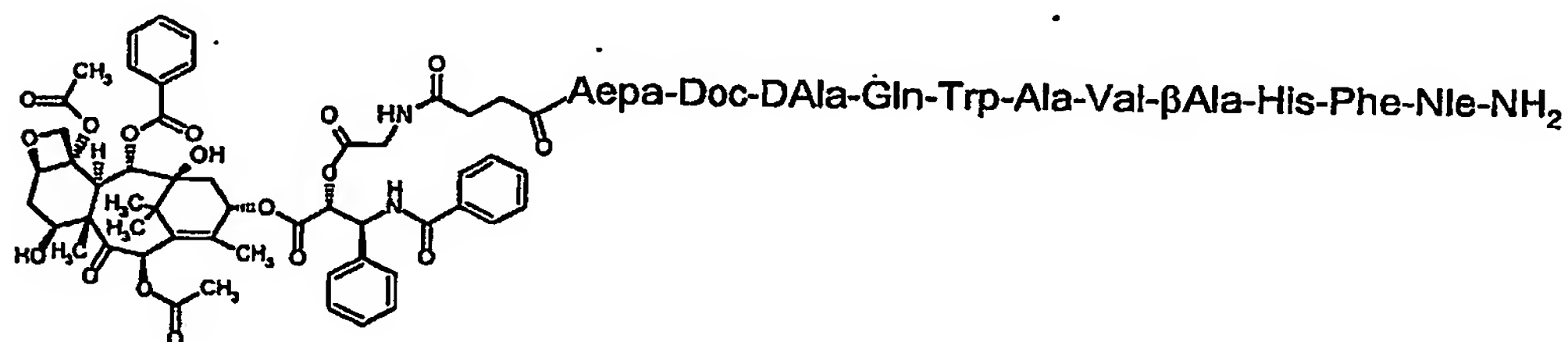
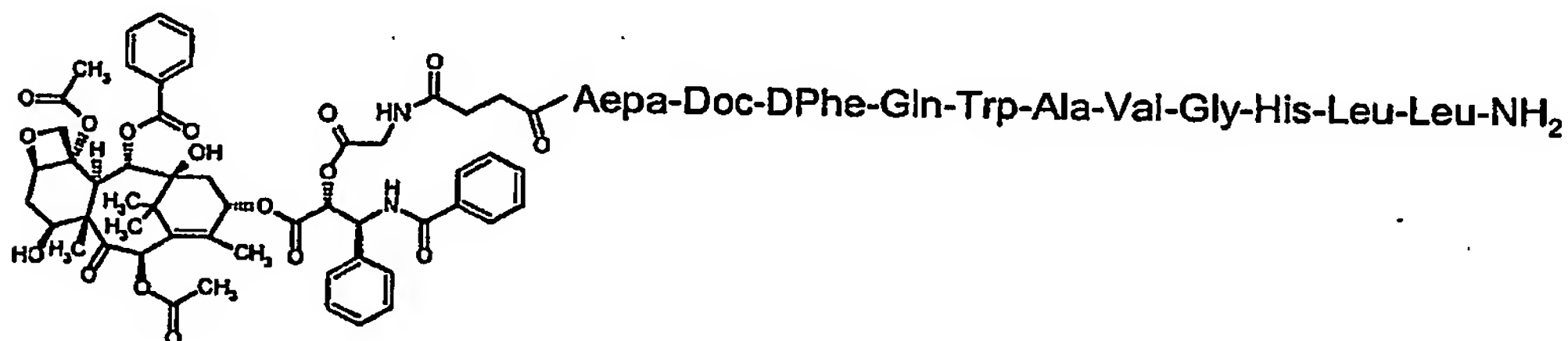
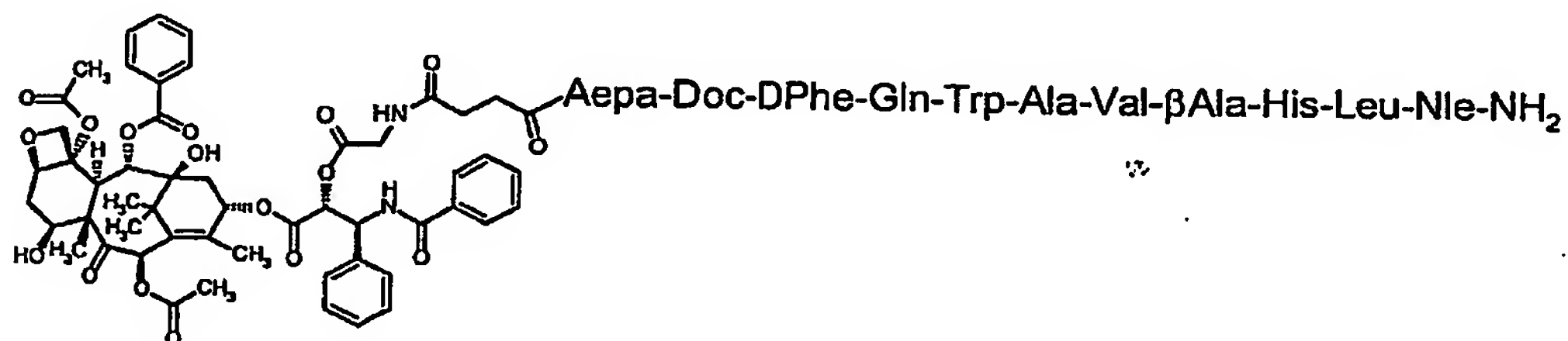
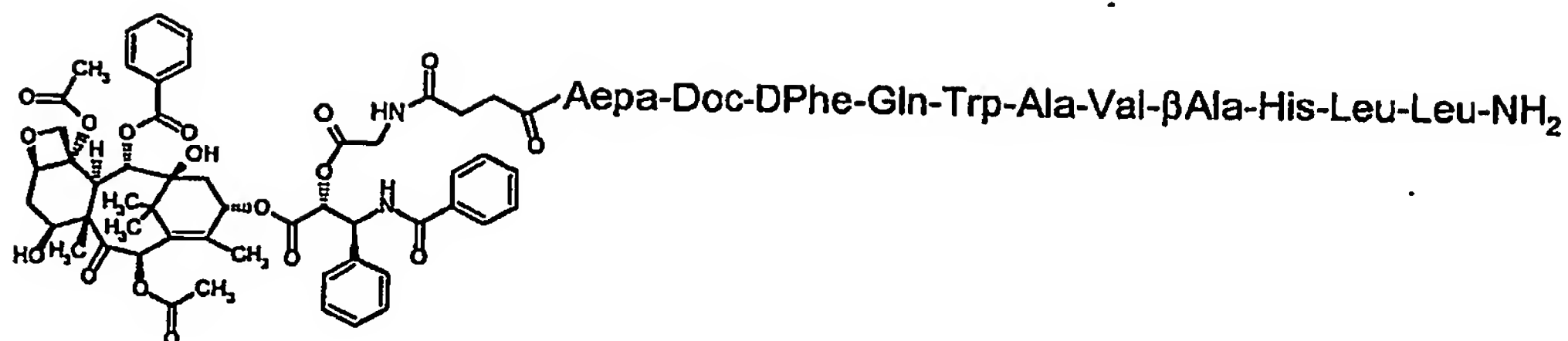


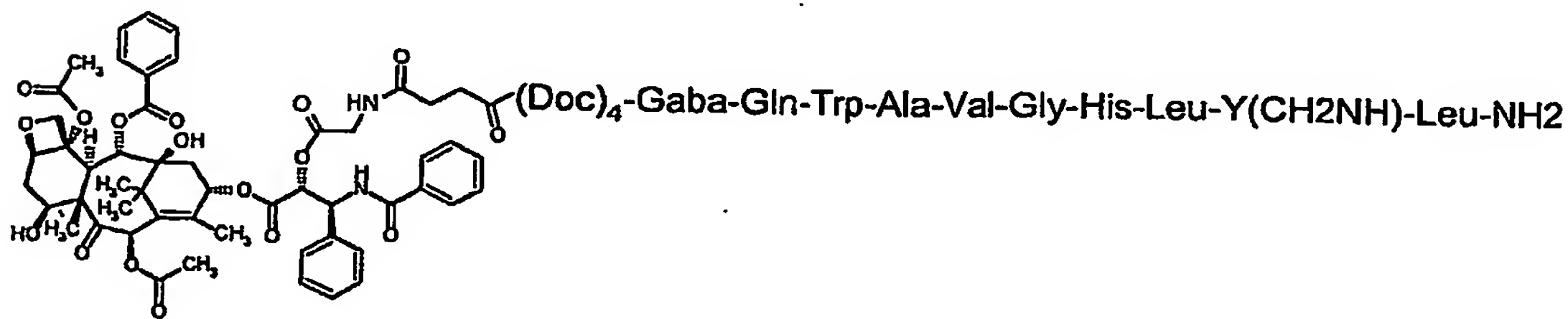
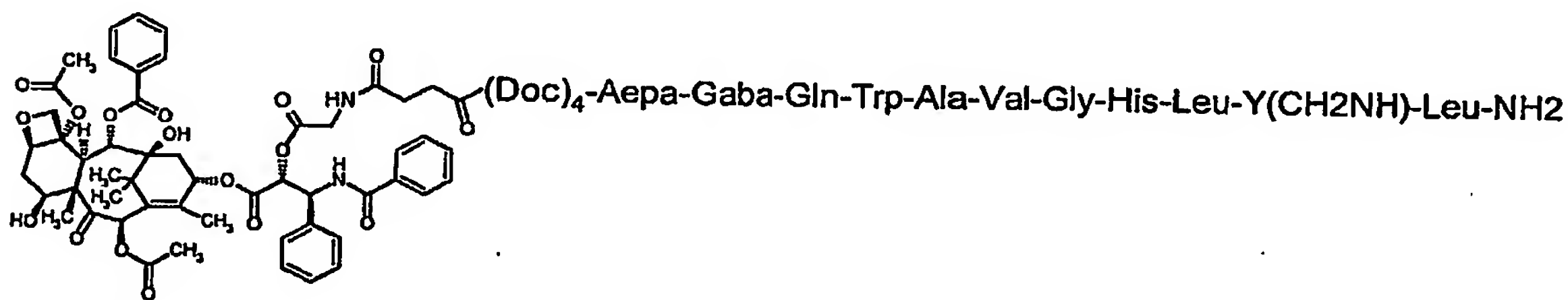
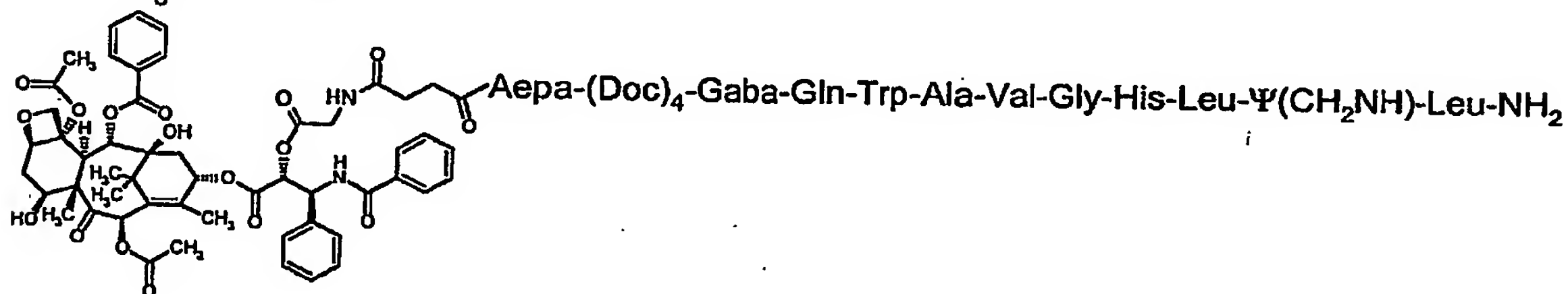
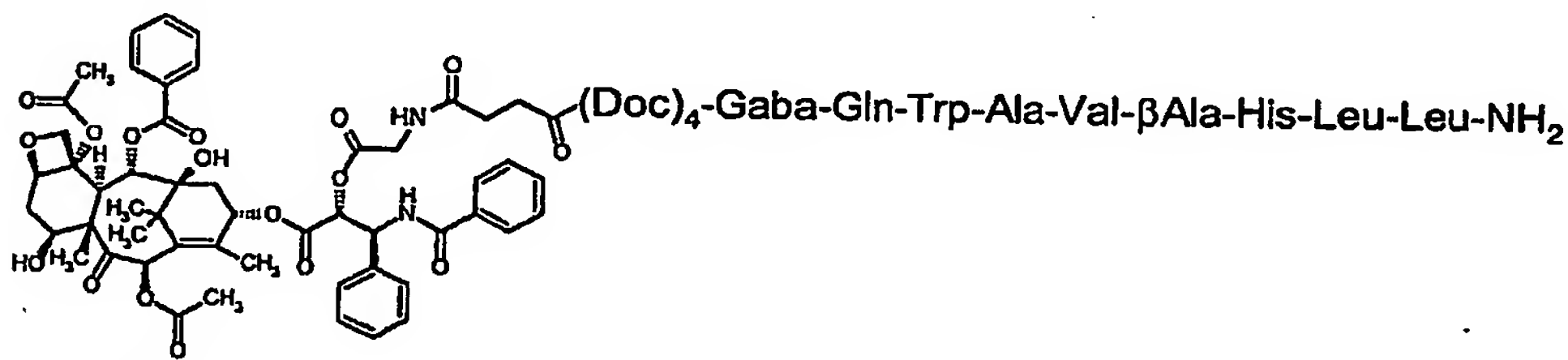
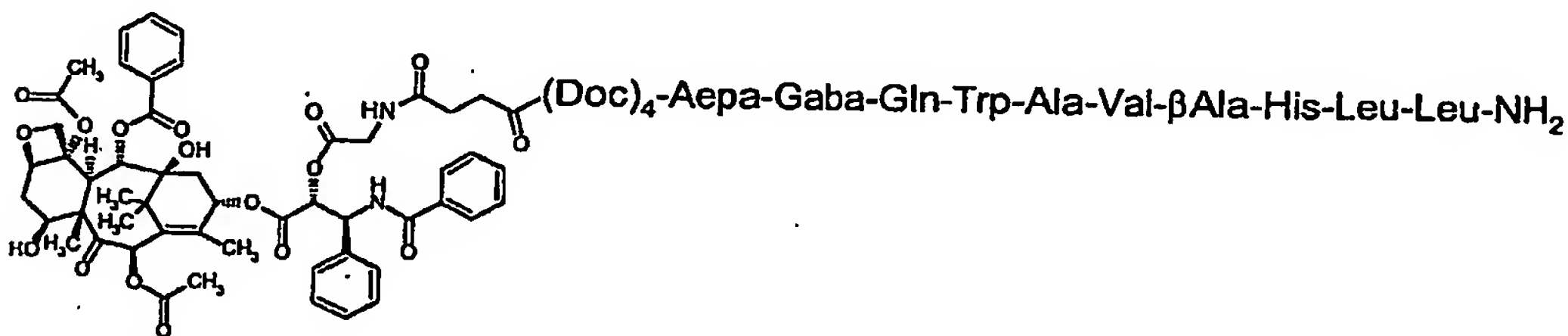
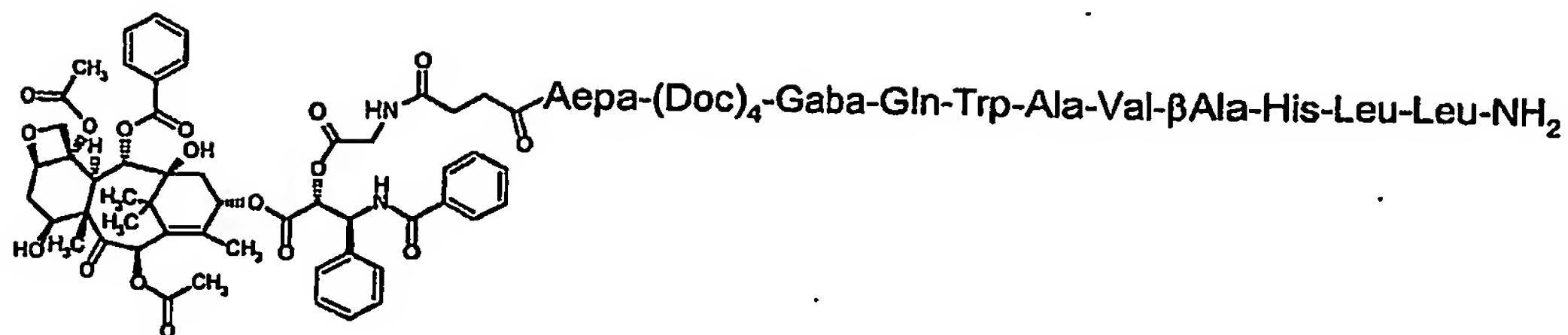
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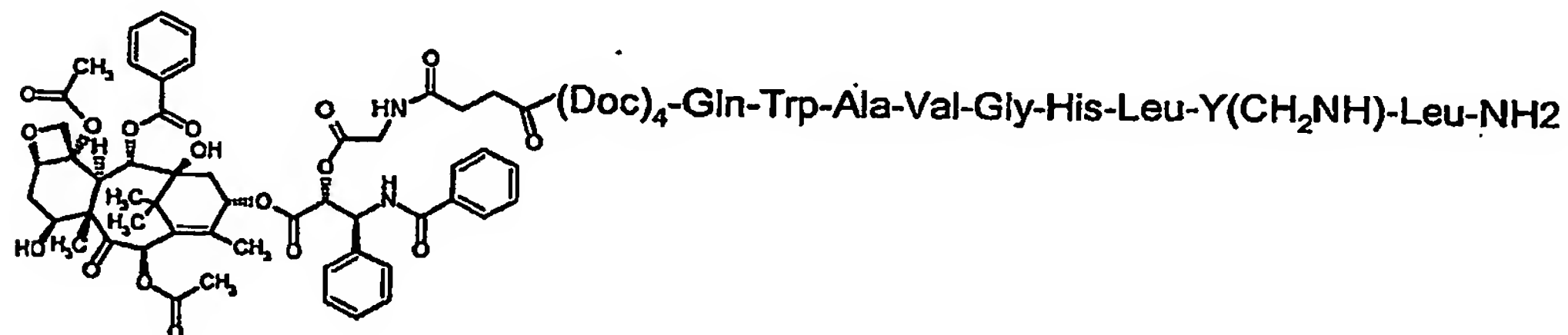
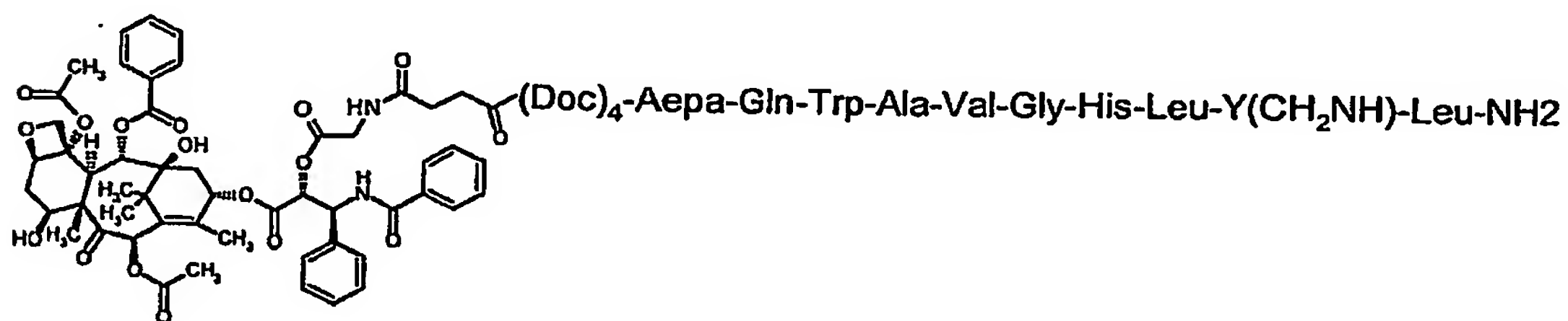
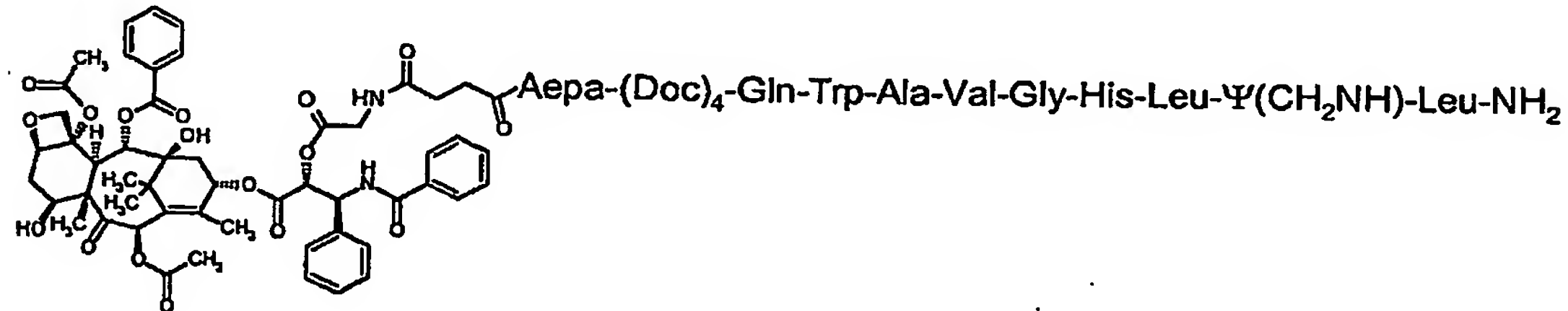
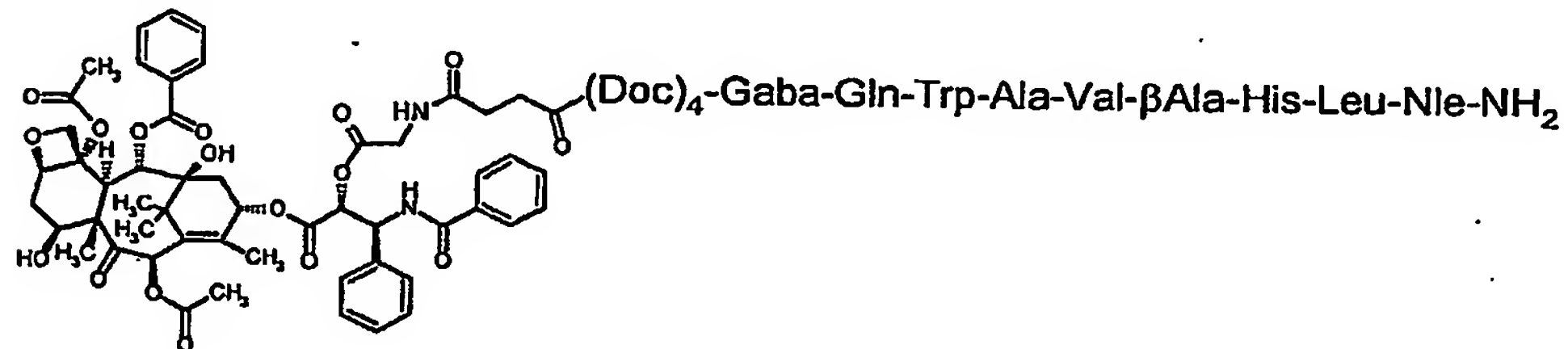
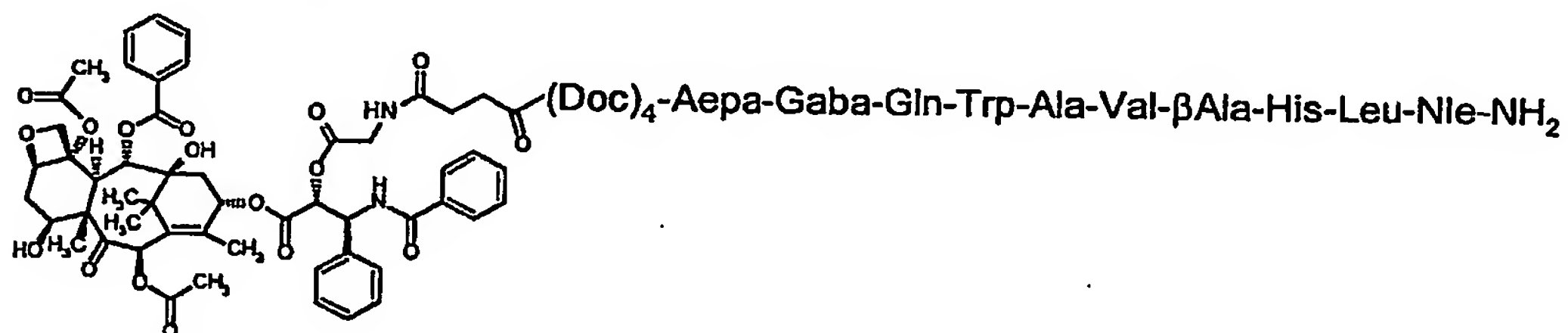
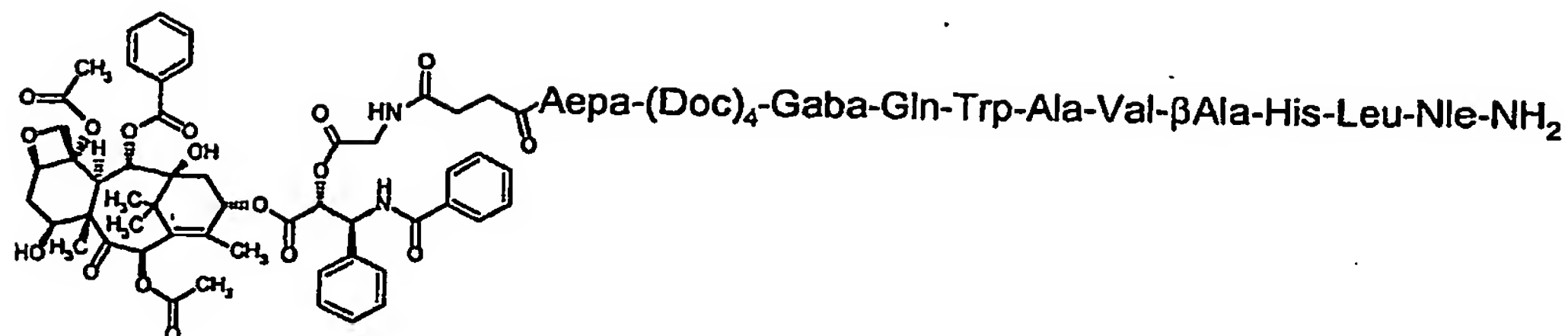


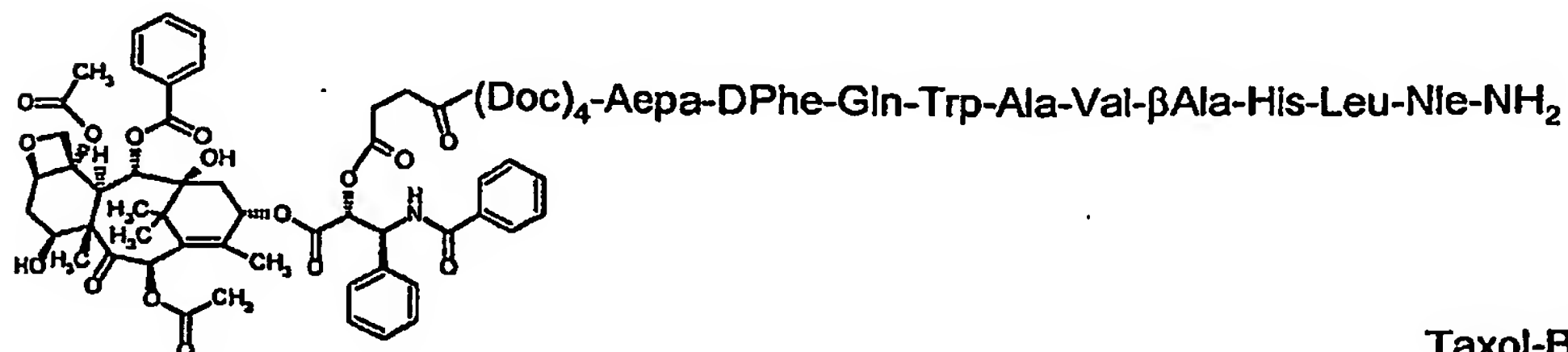
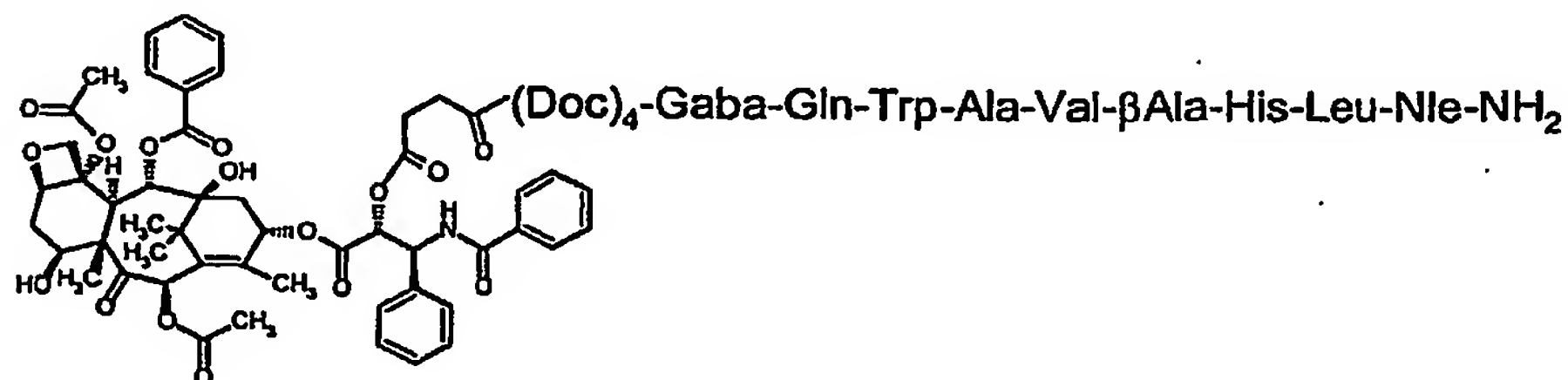
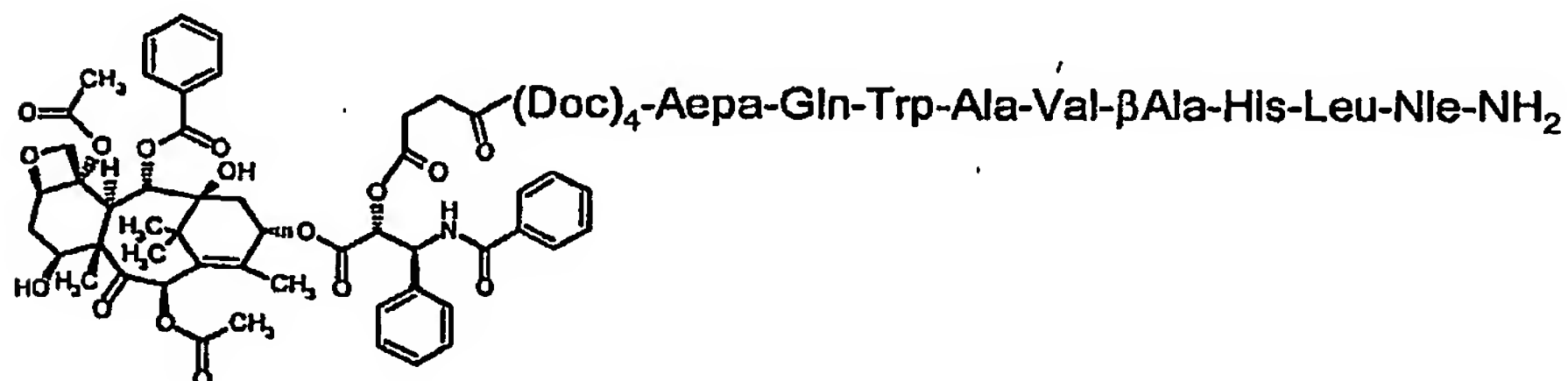
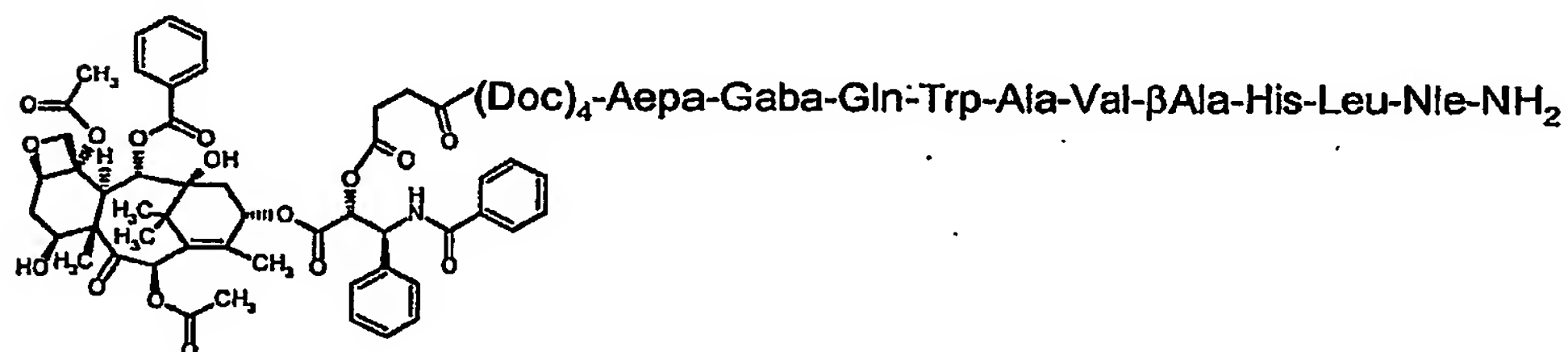
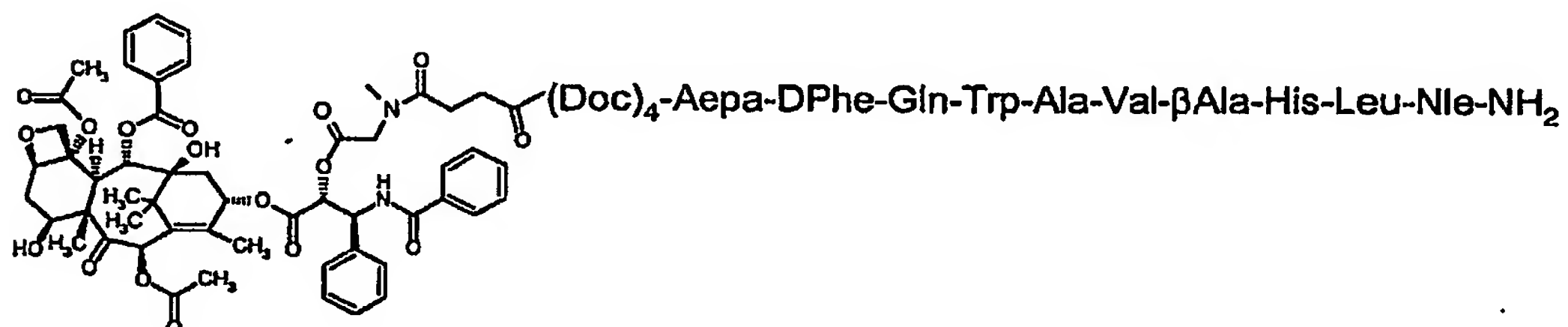
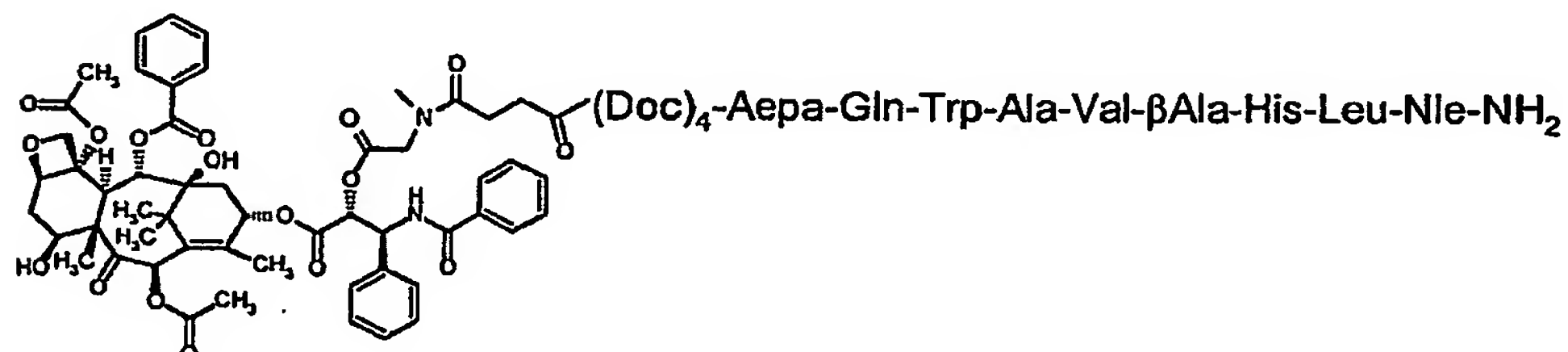
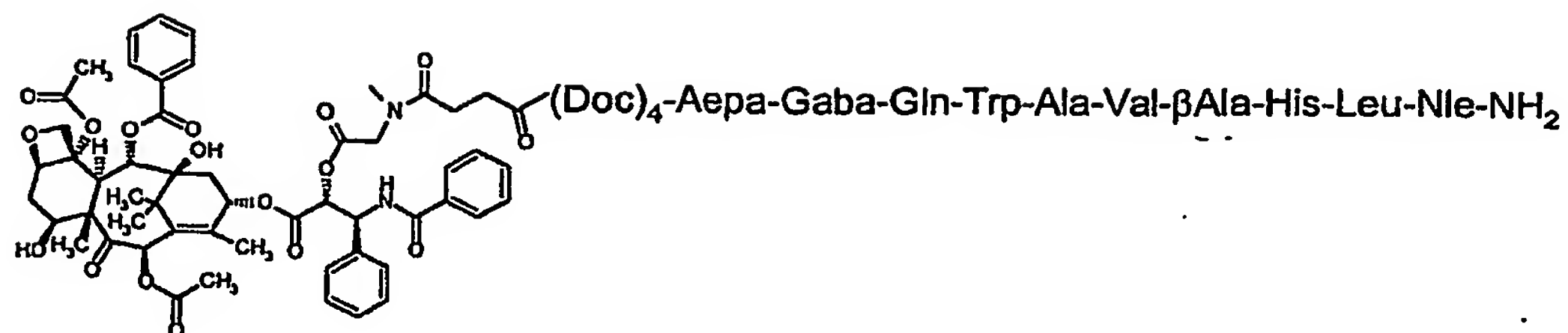




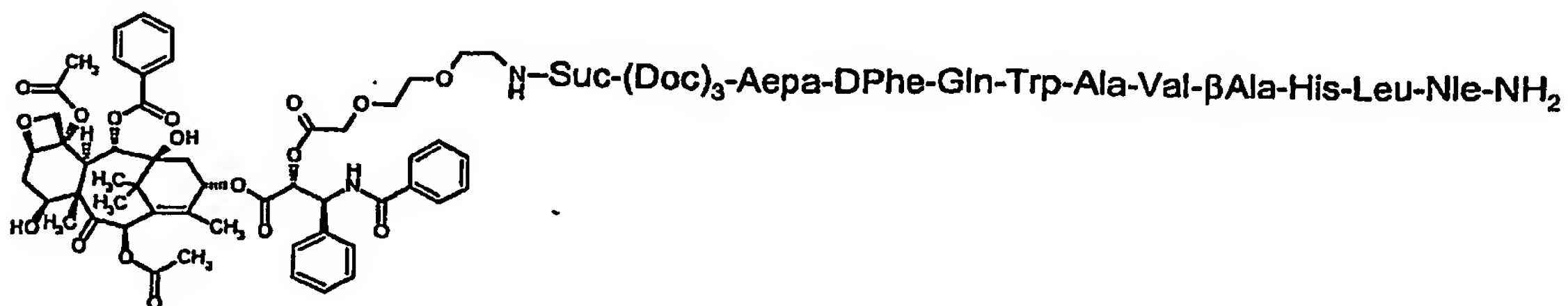
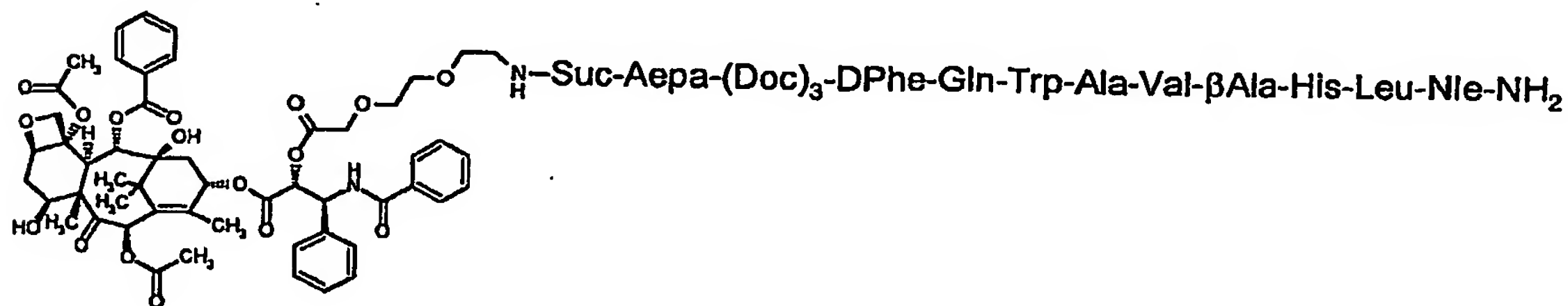
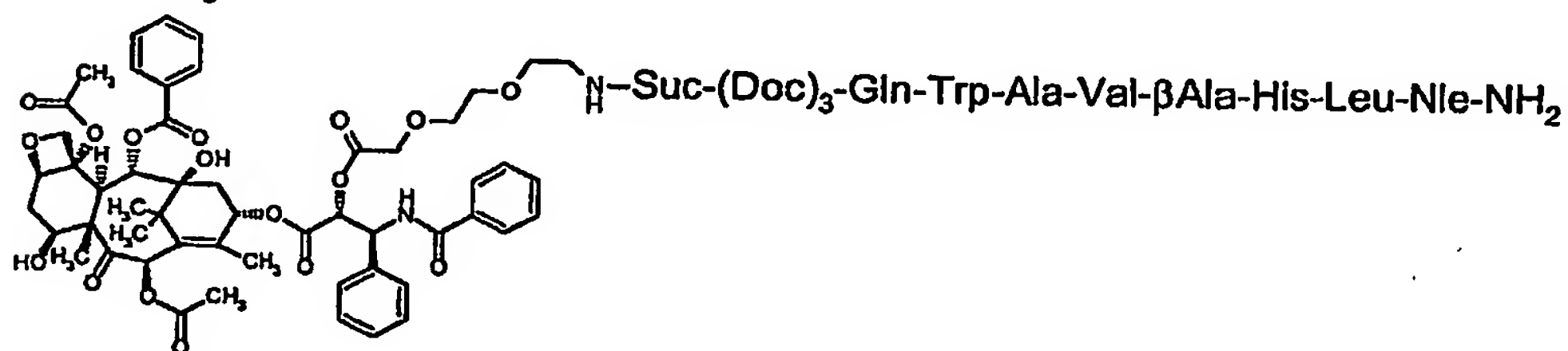
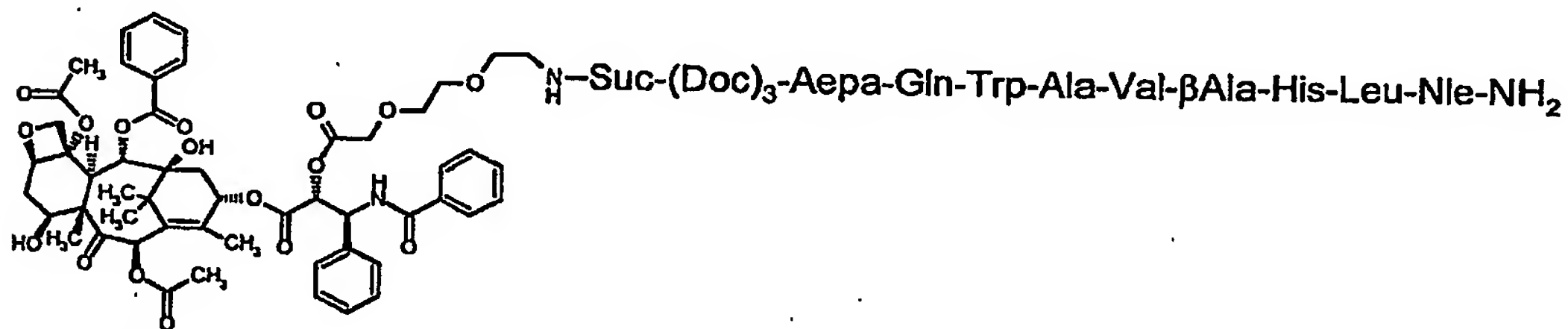
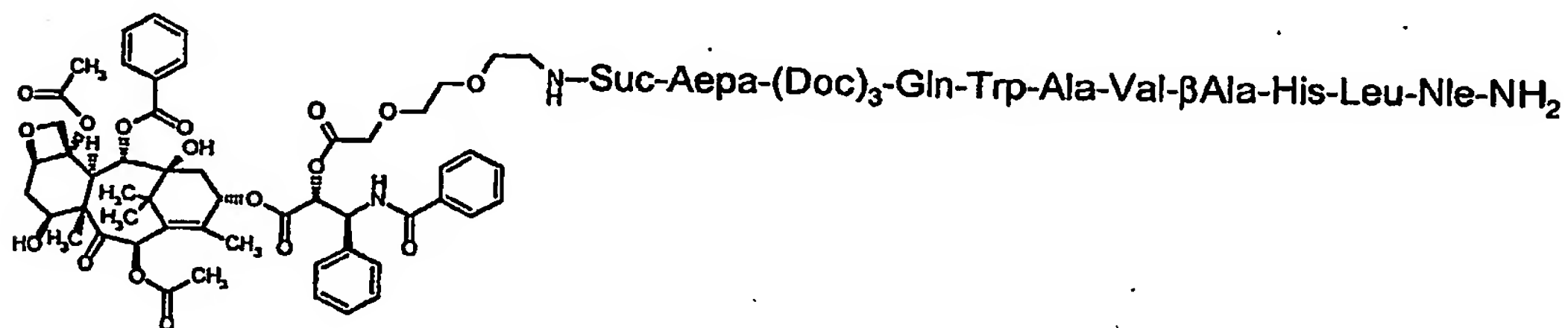
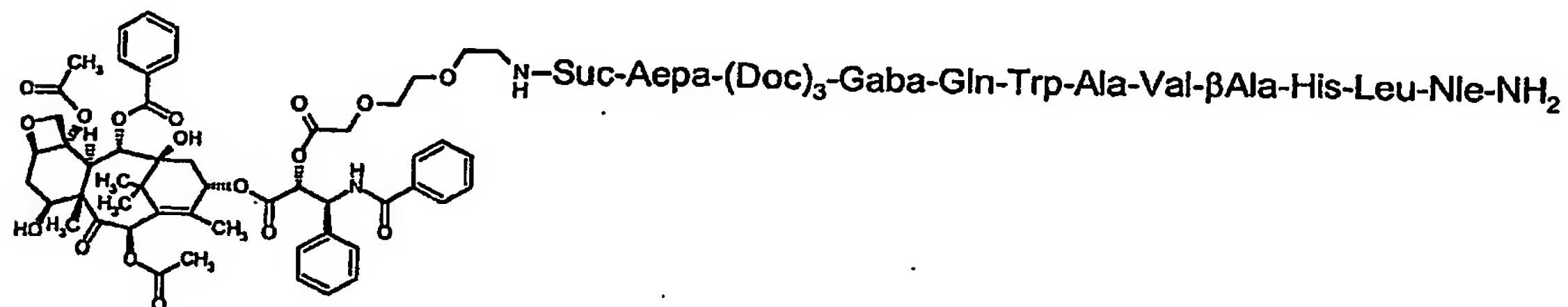
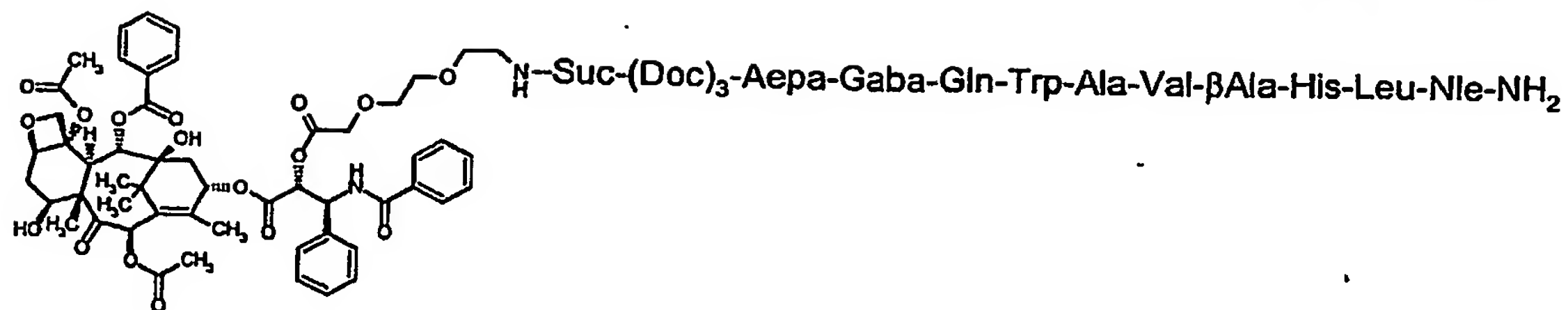


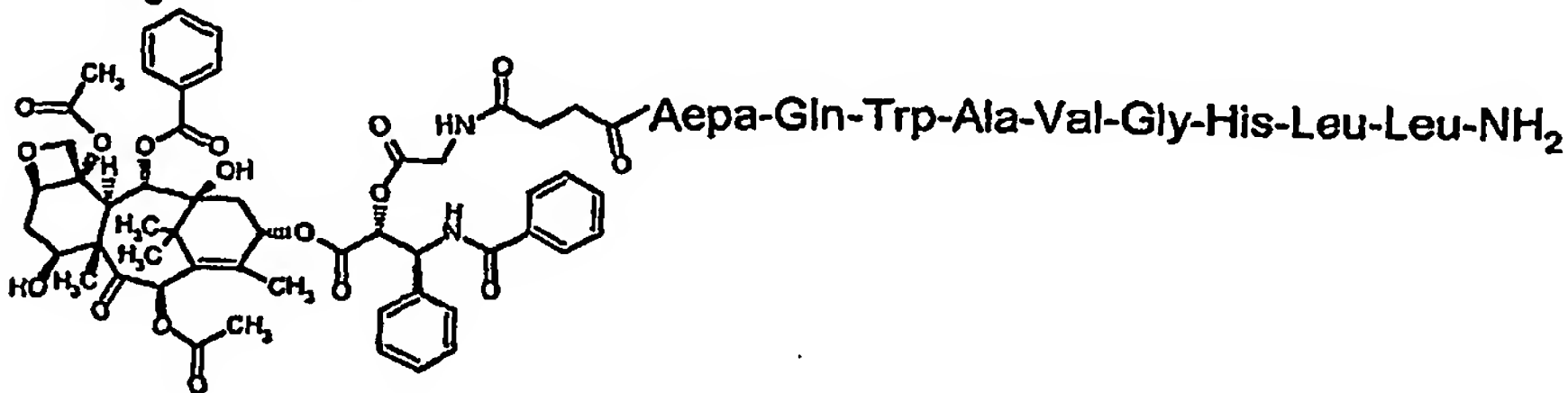
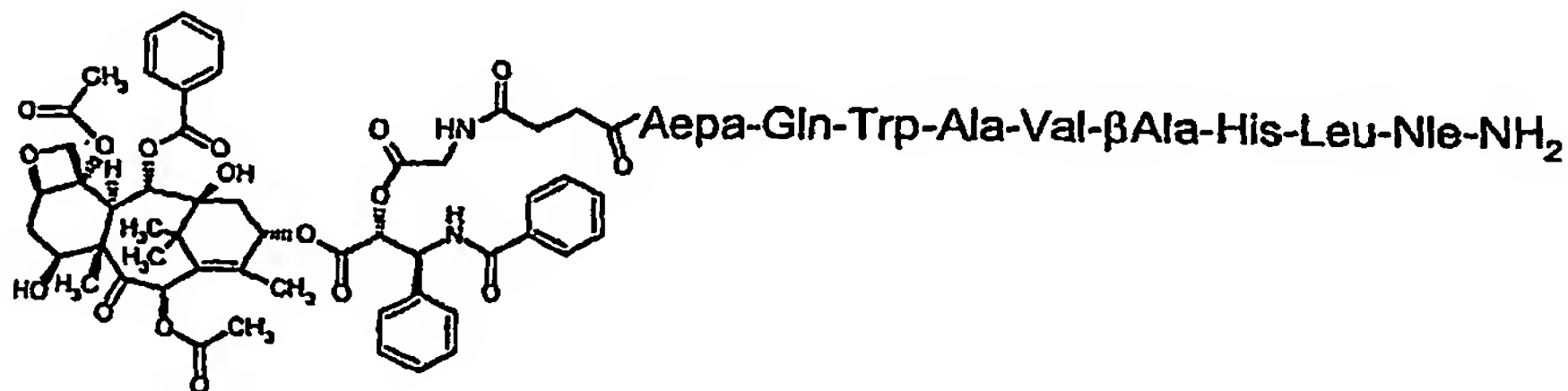
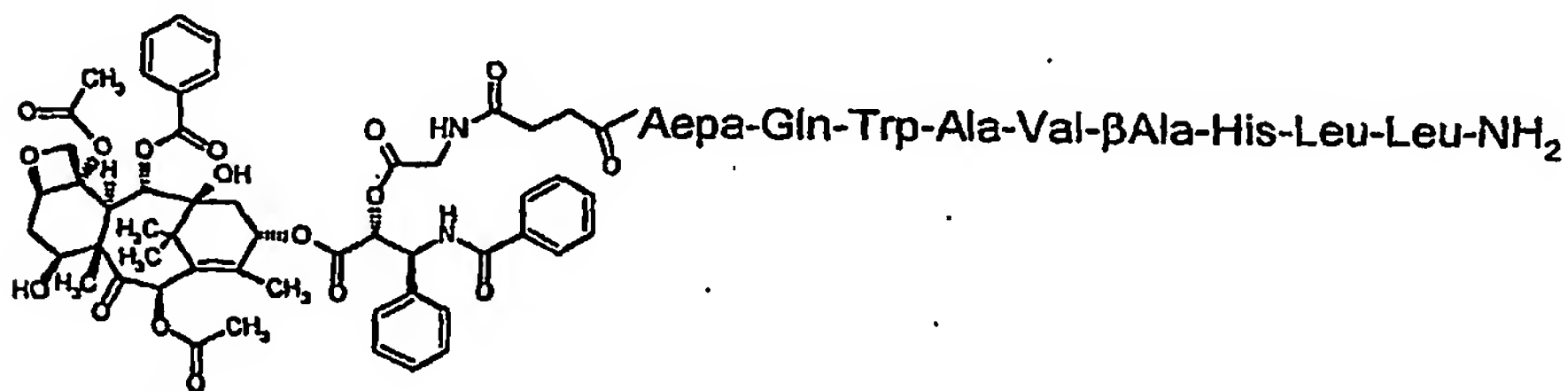
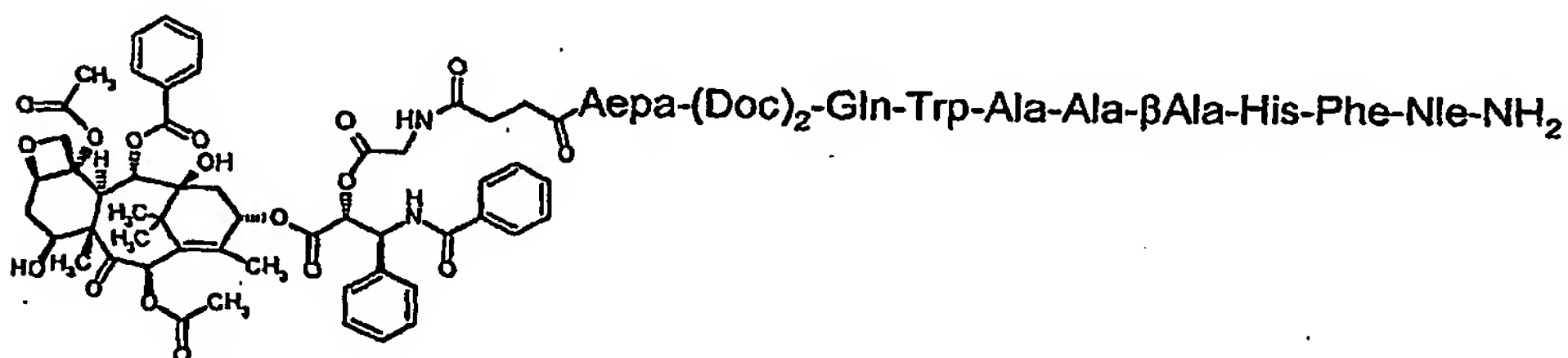
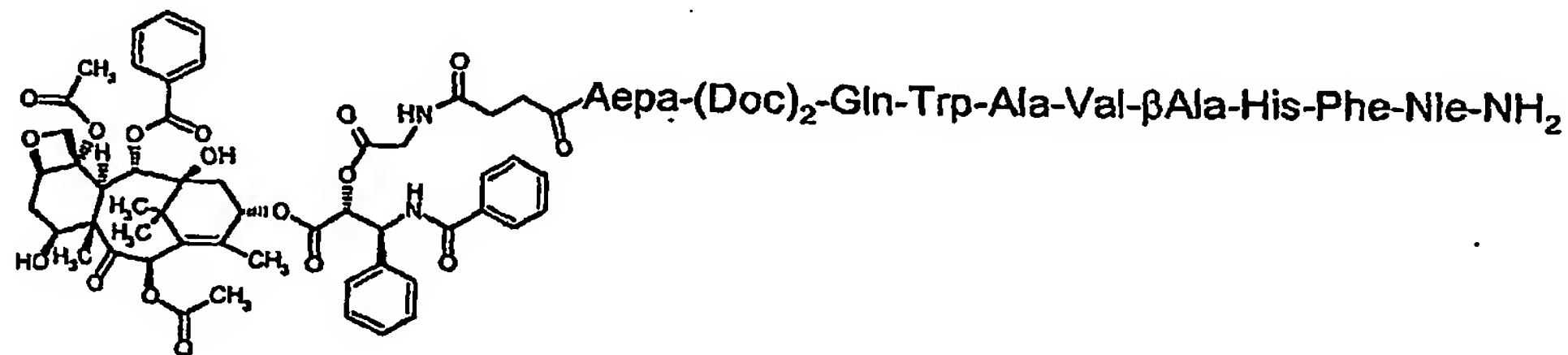
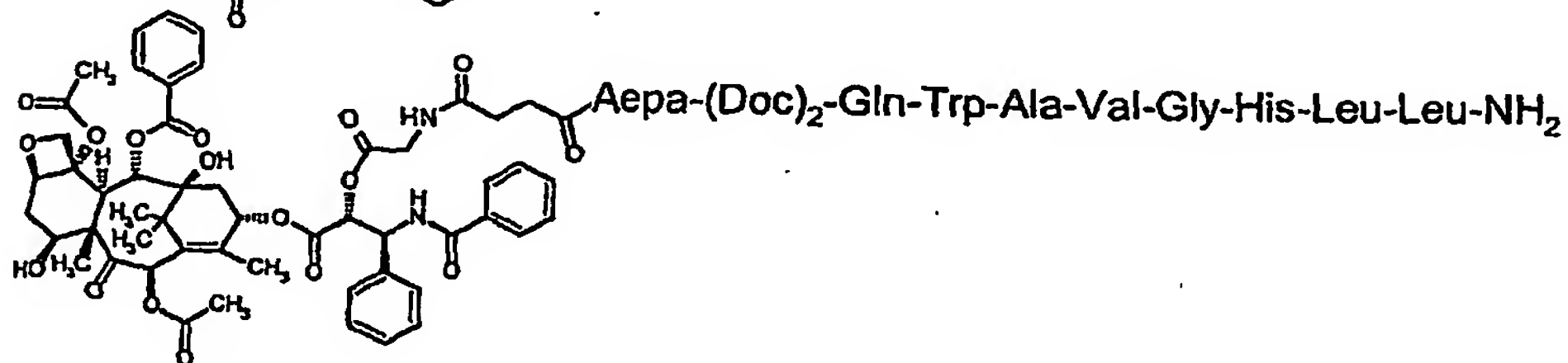
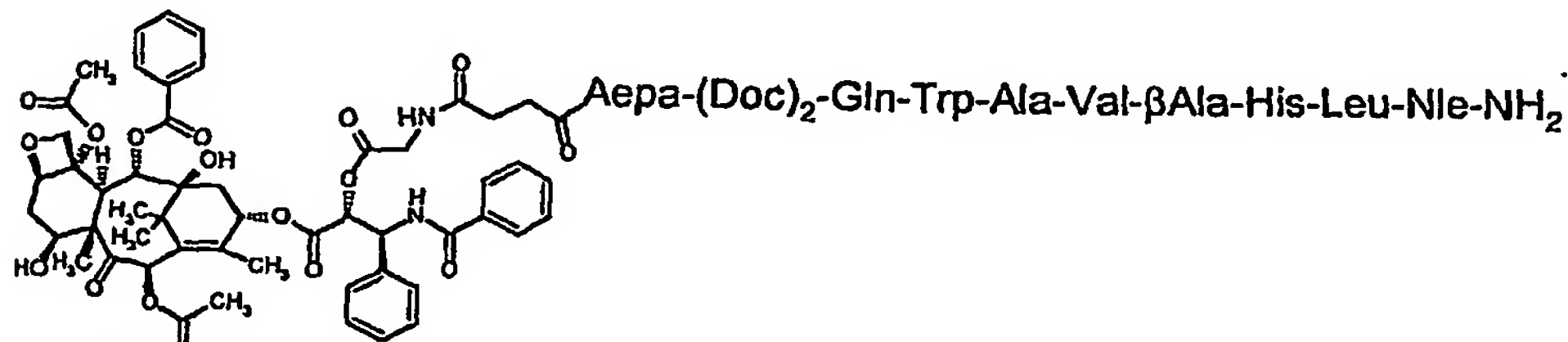
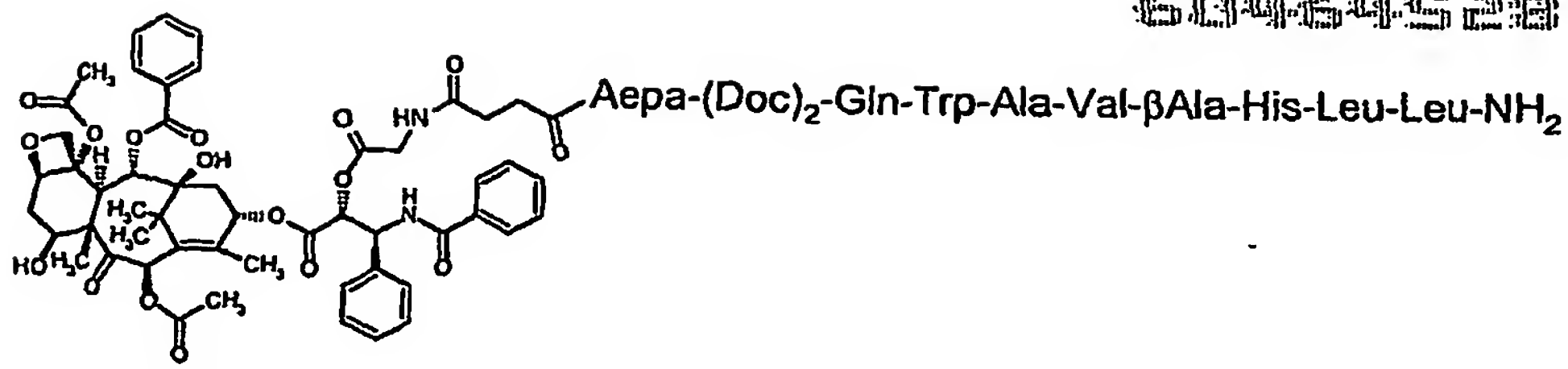


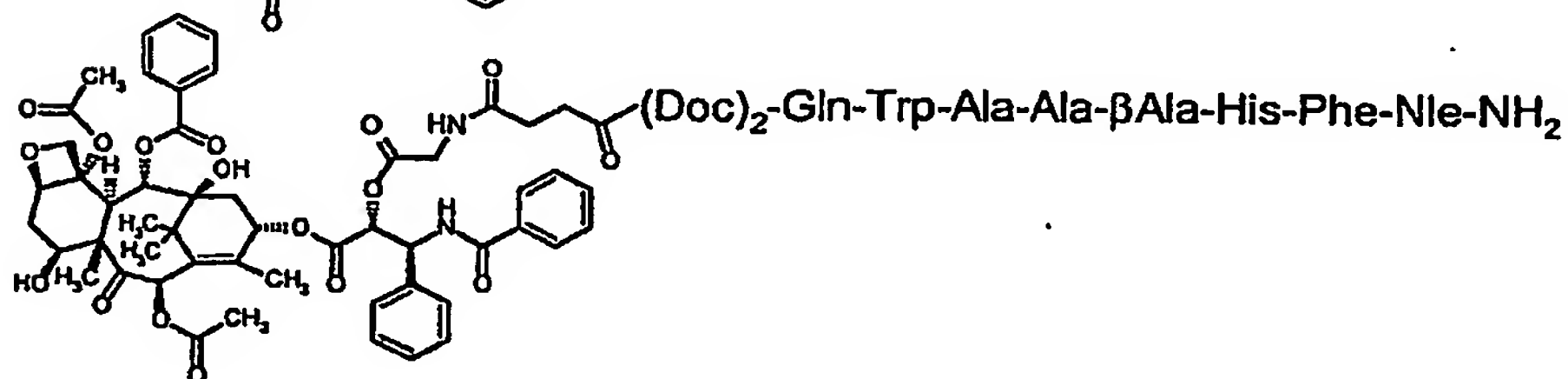
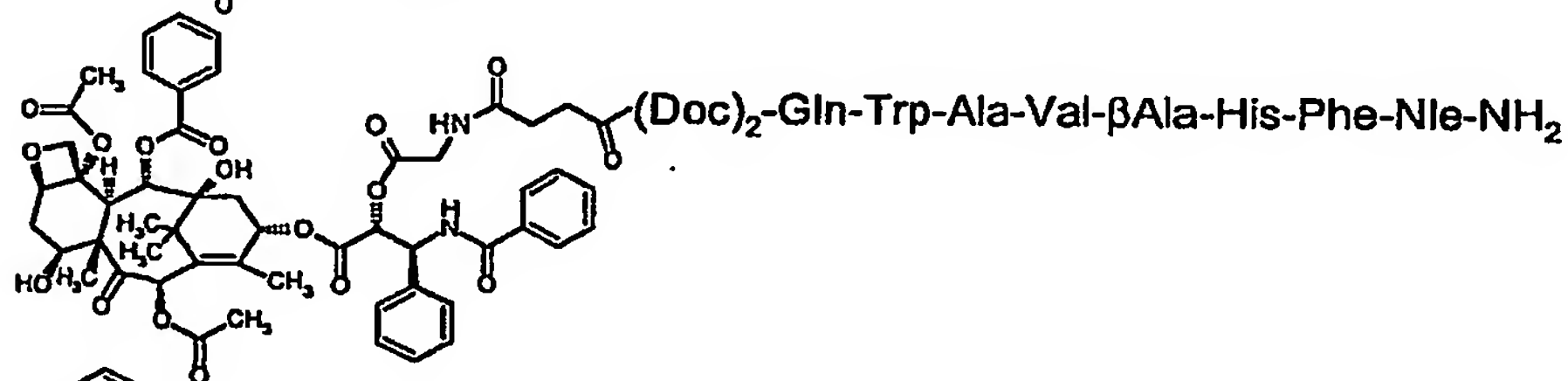
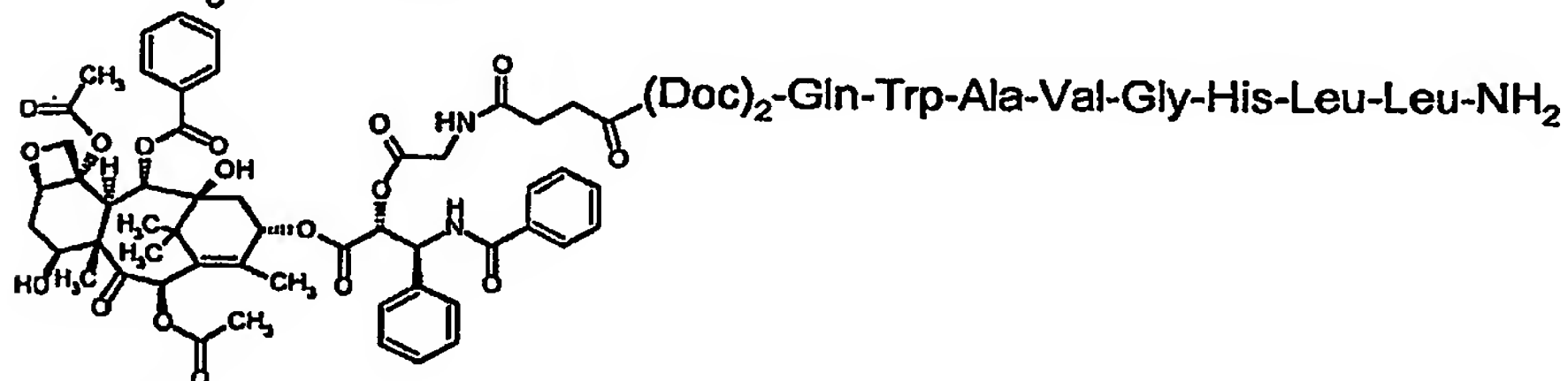
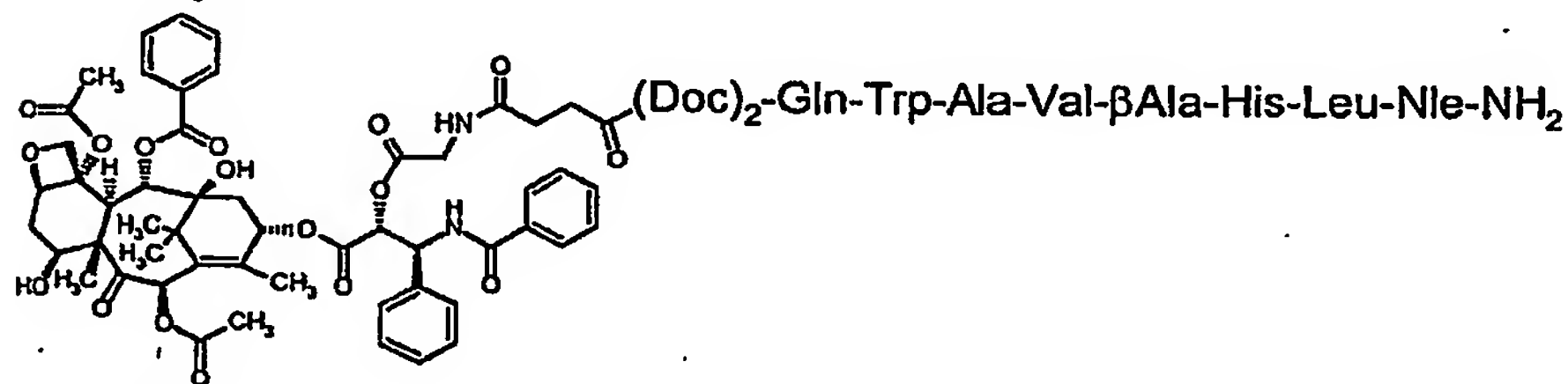
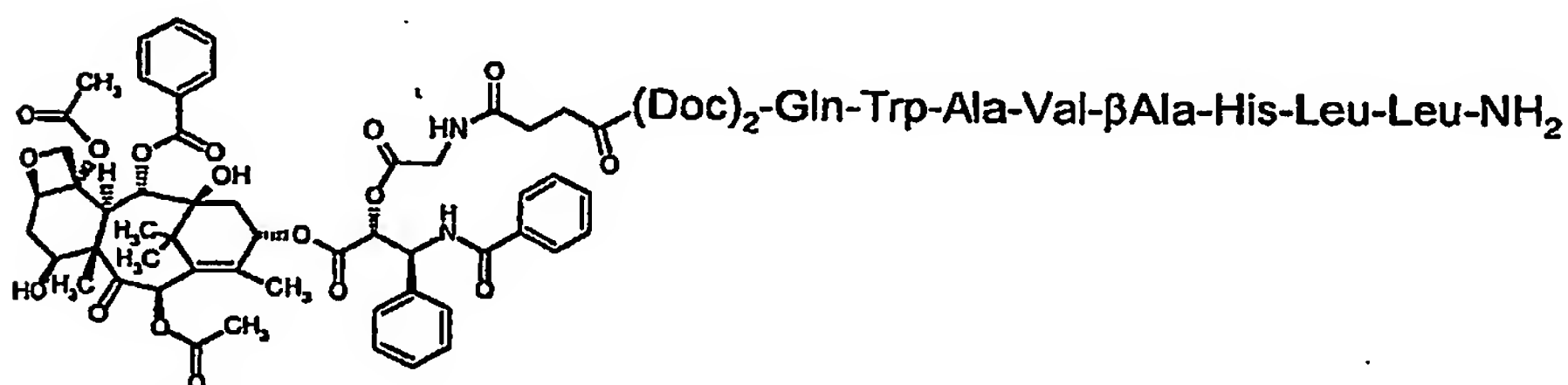
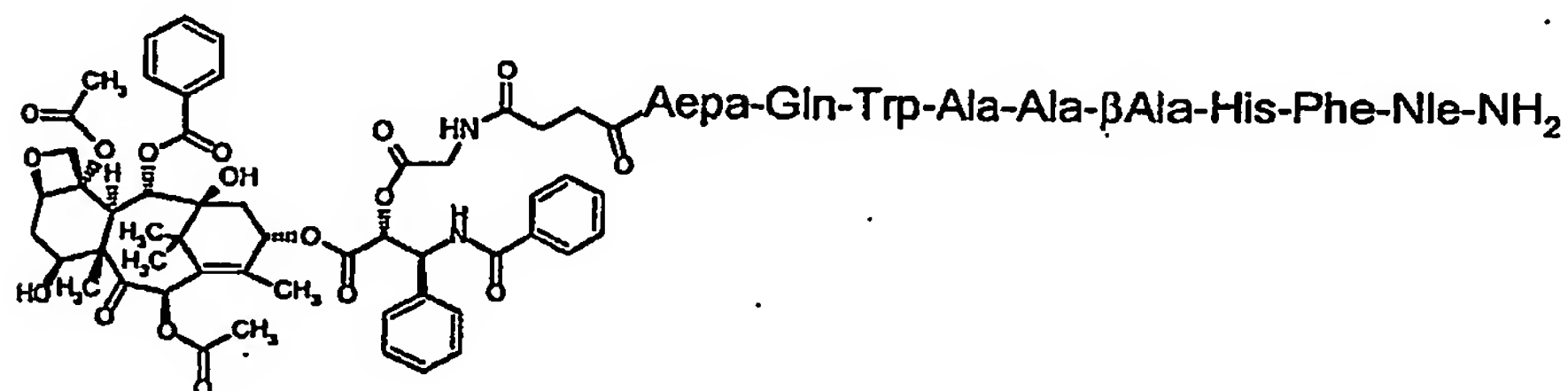
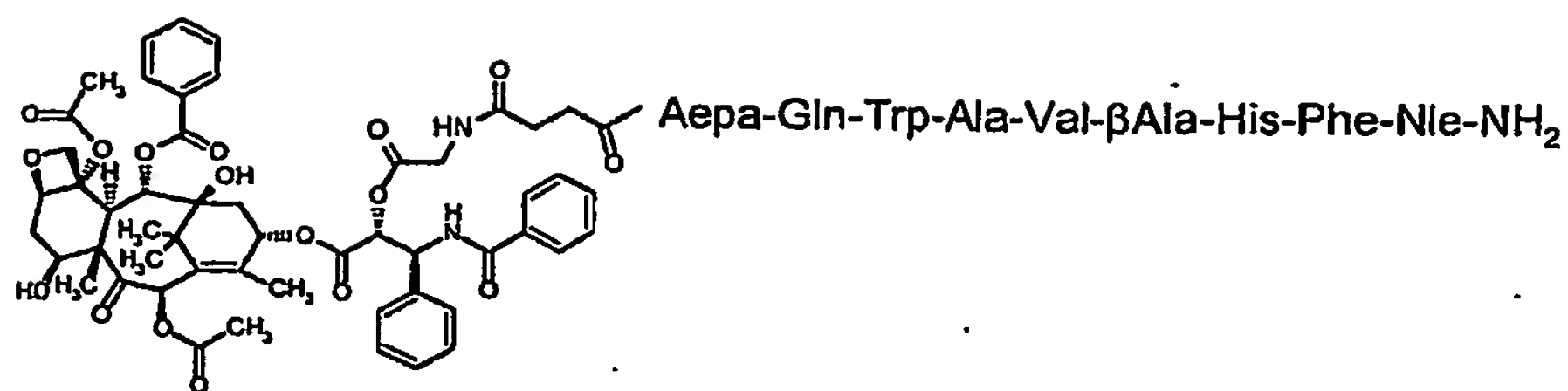


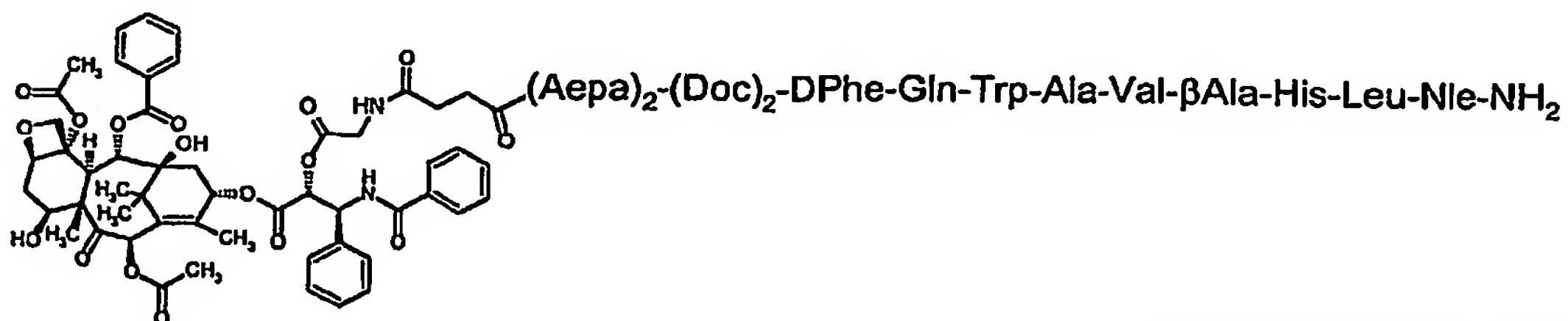
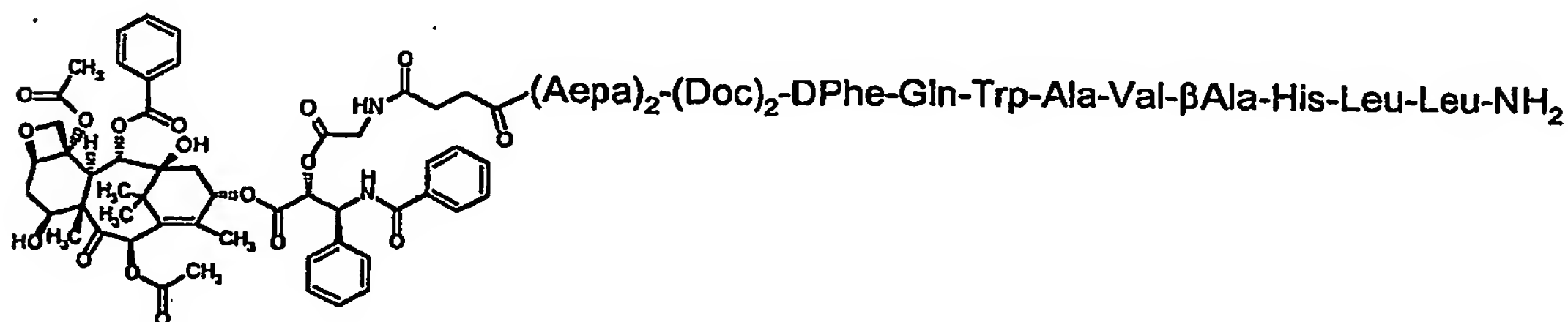
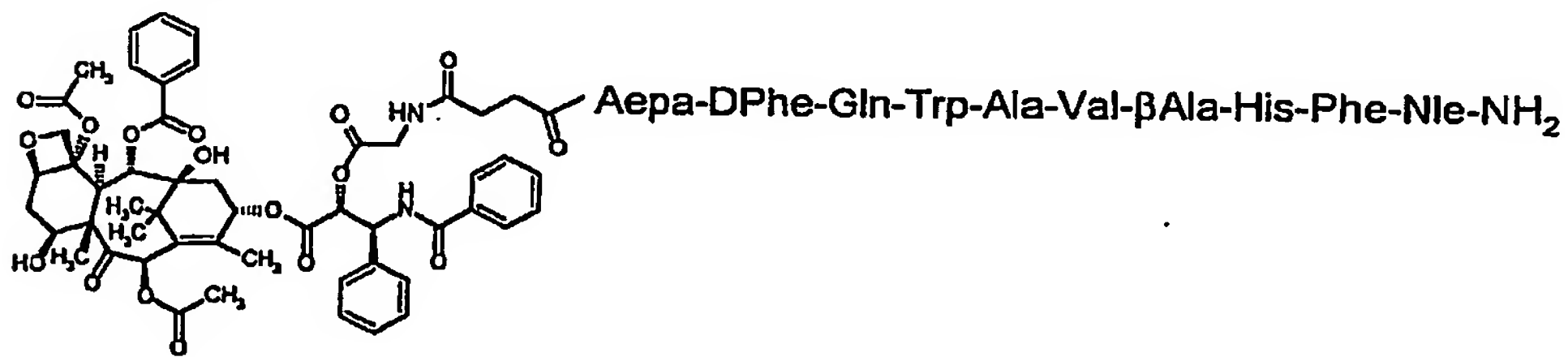
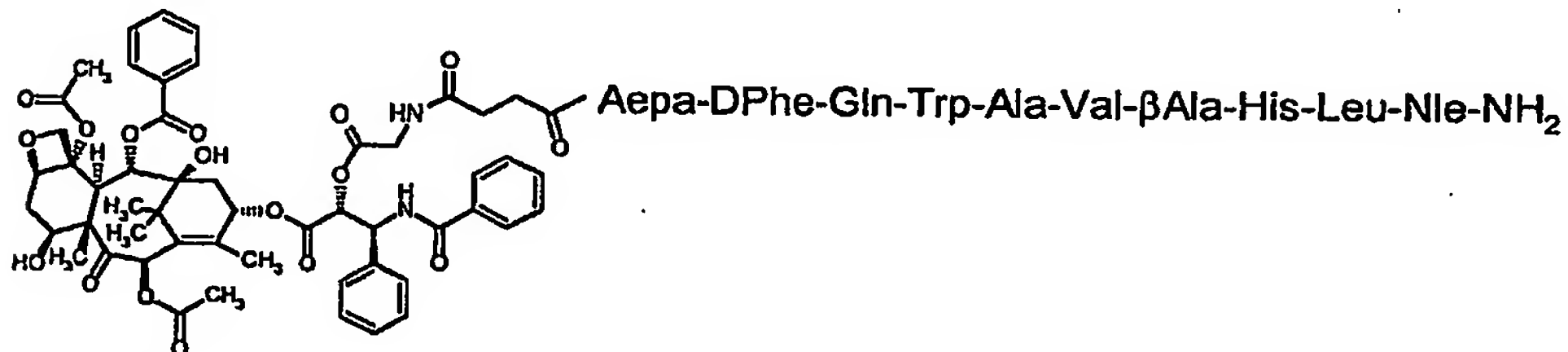
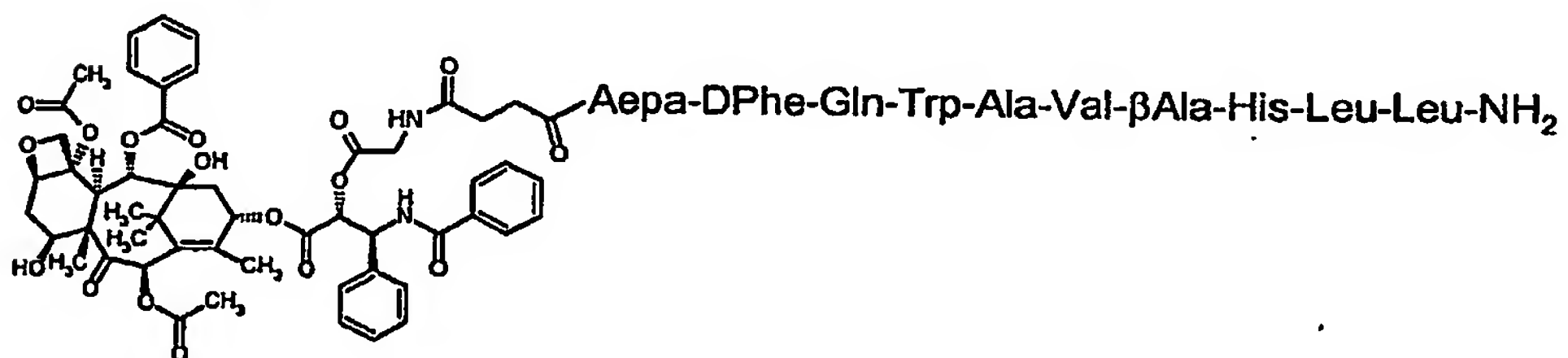
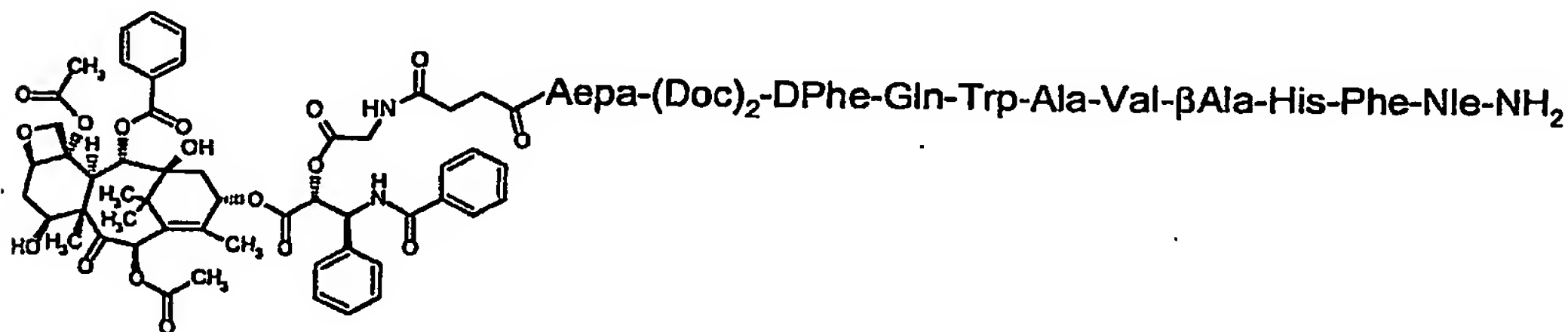
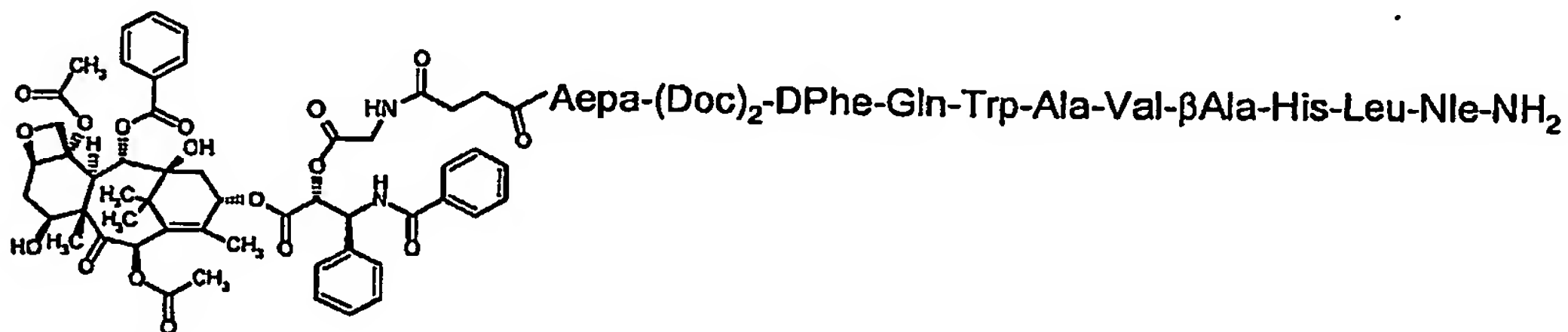
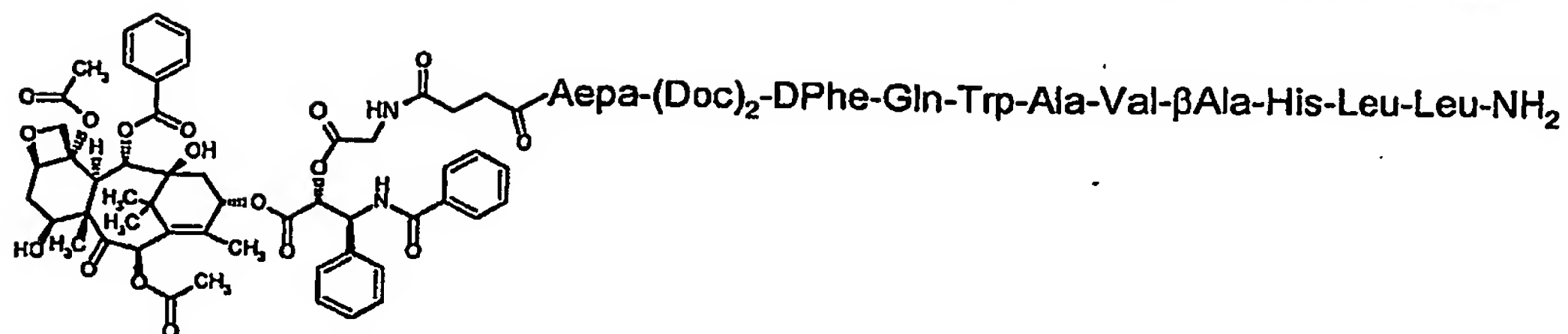


Appendix H

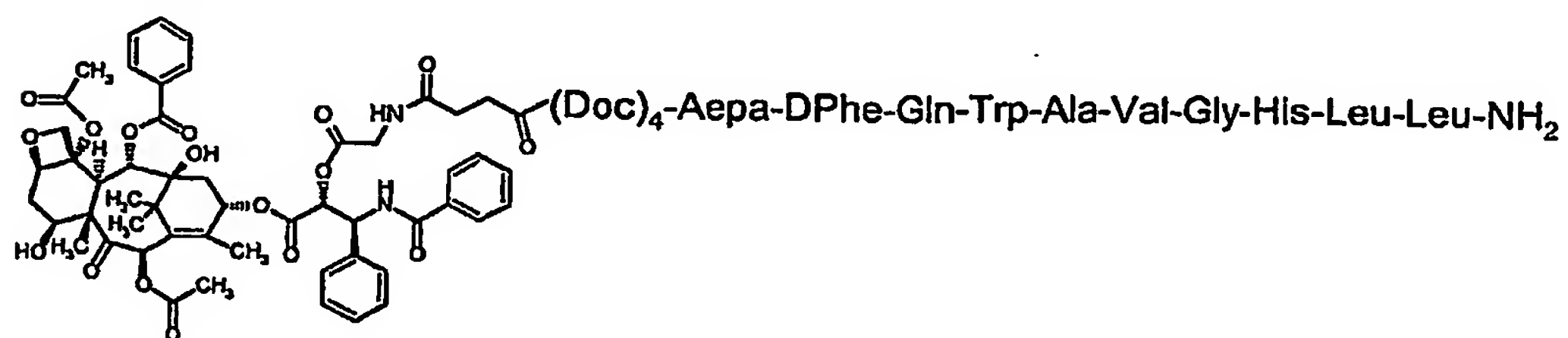
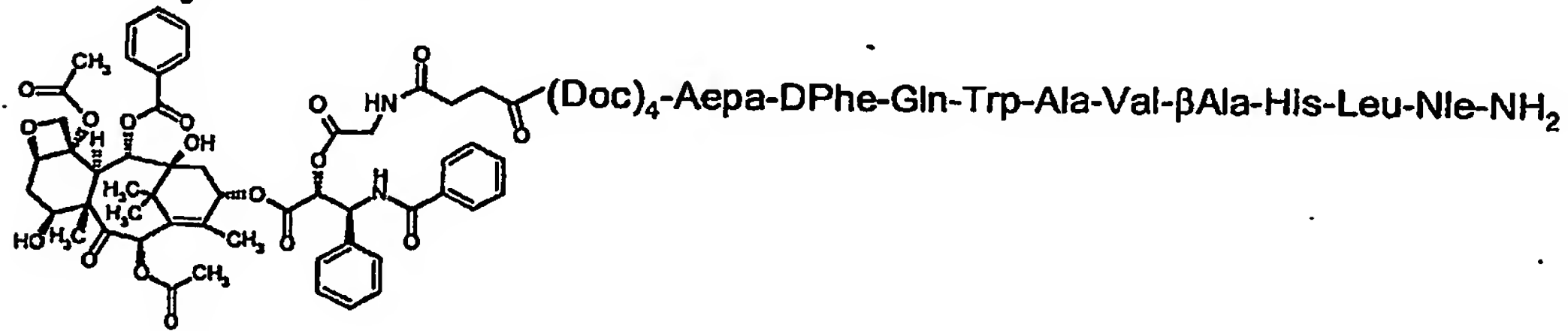
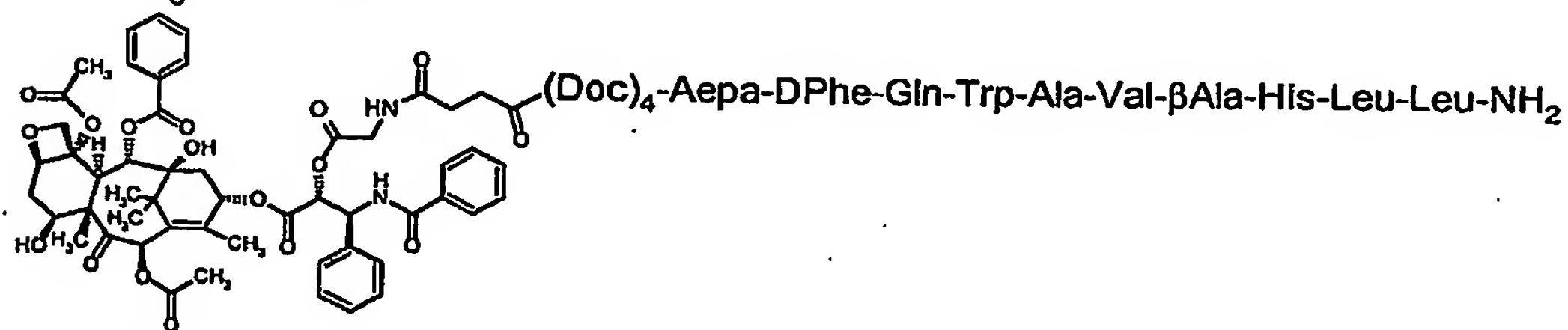
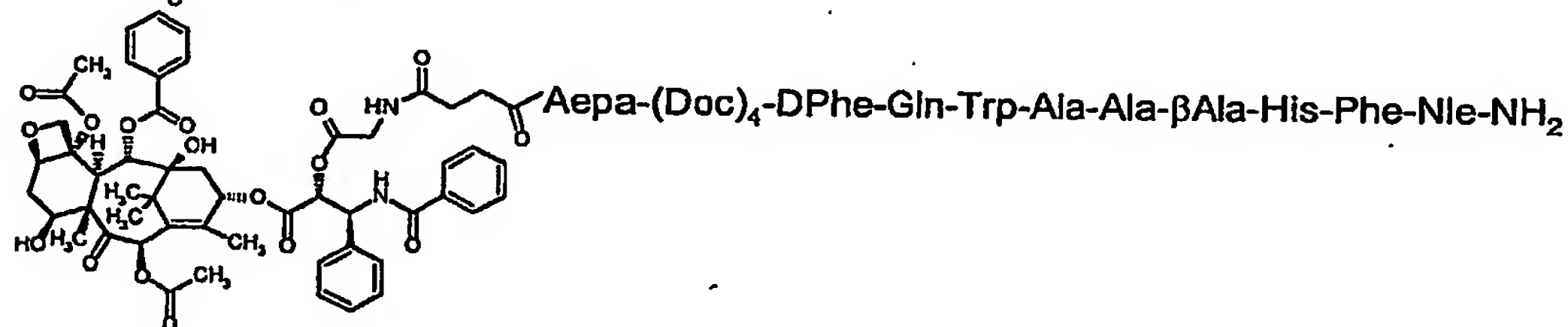
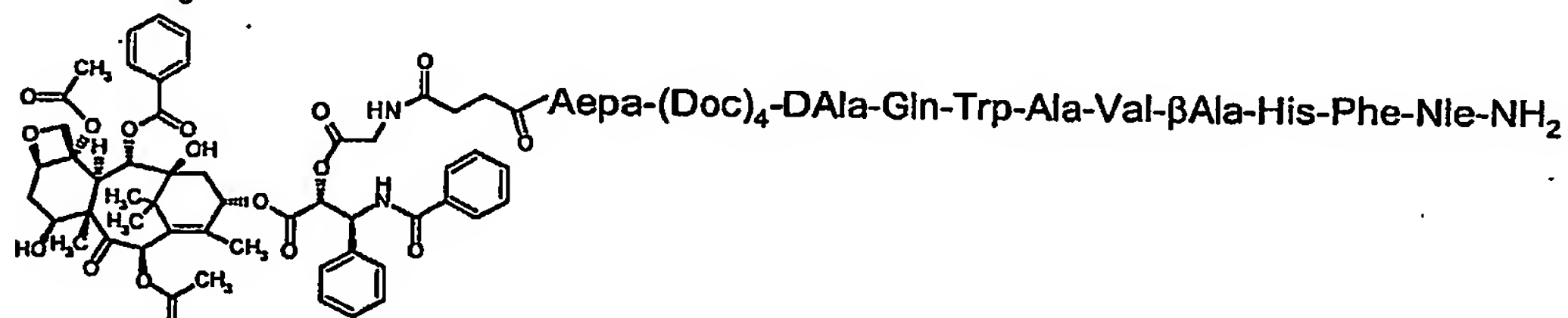
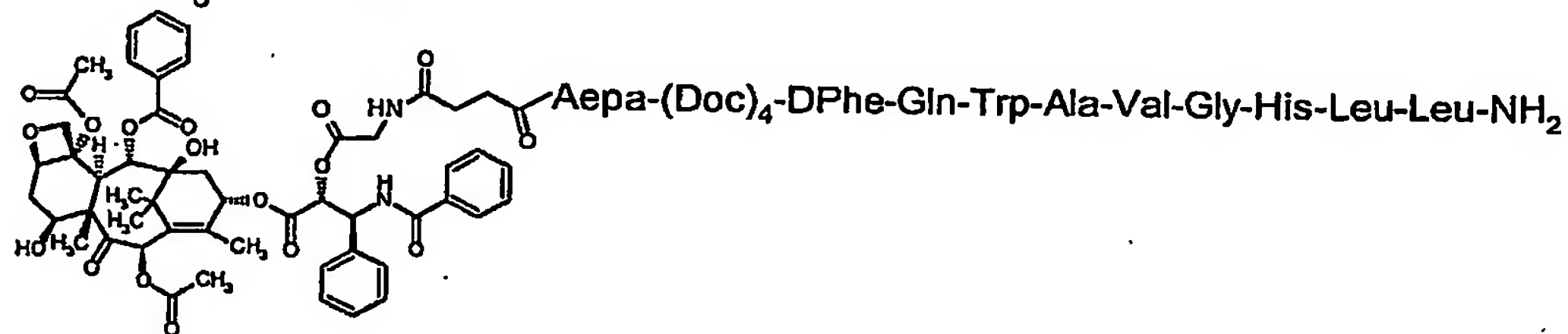
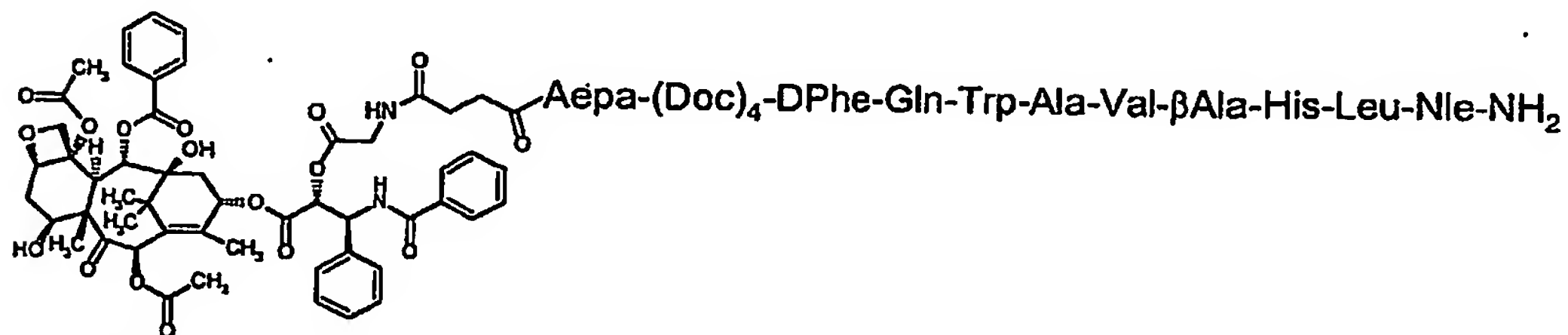
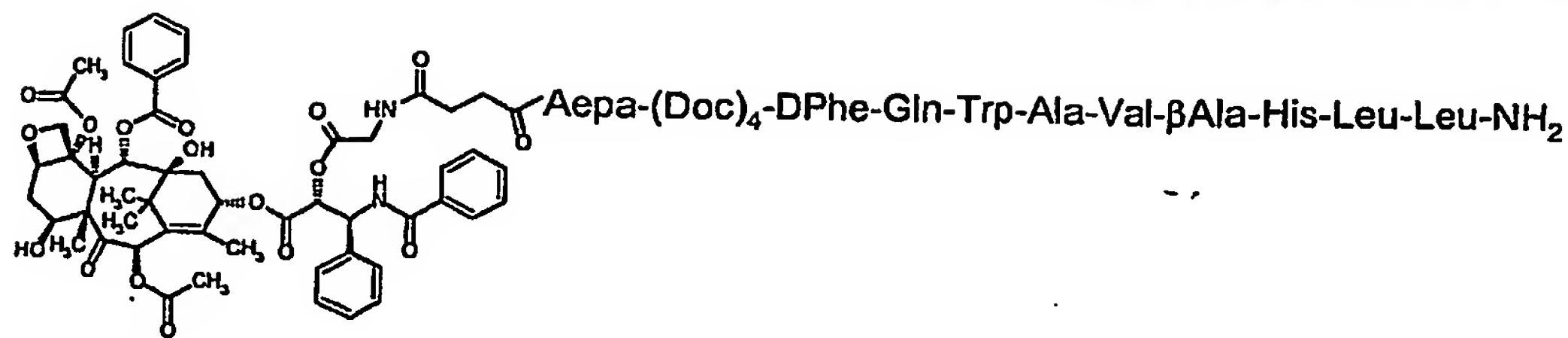


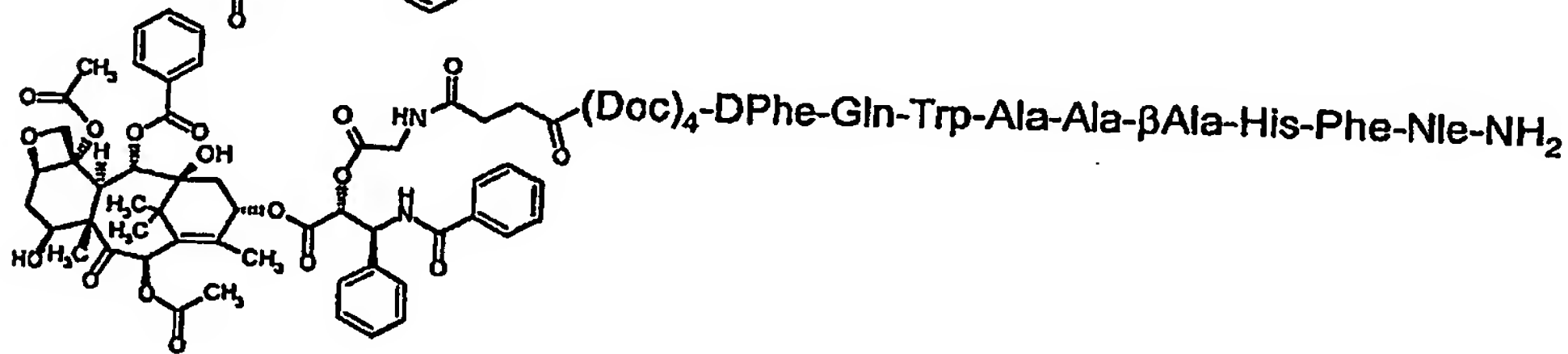
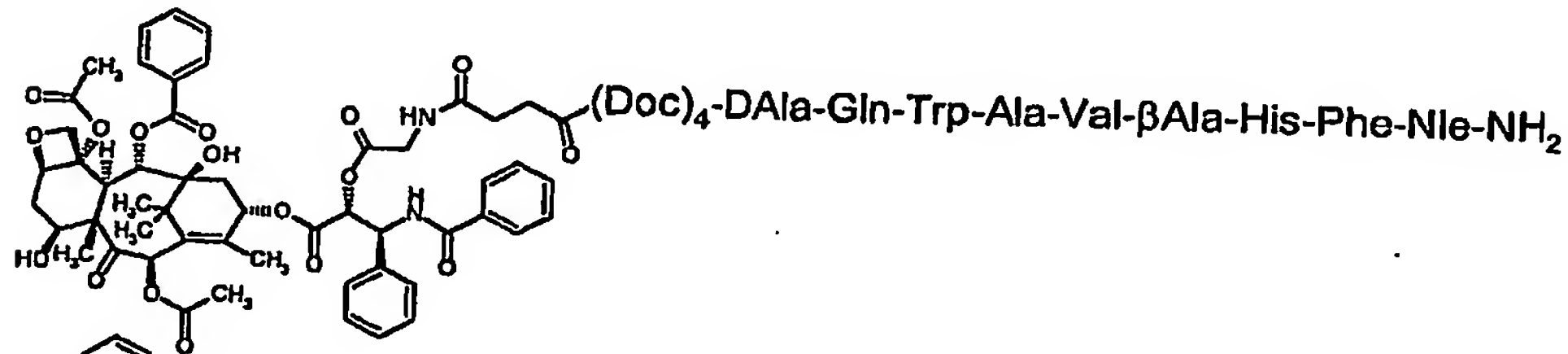
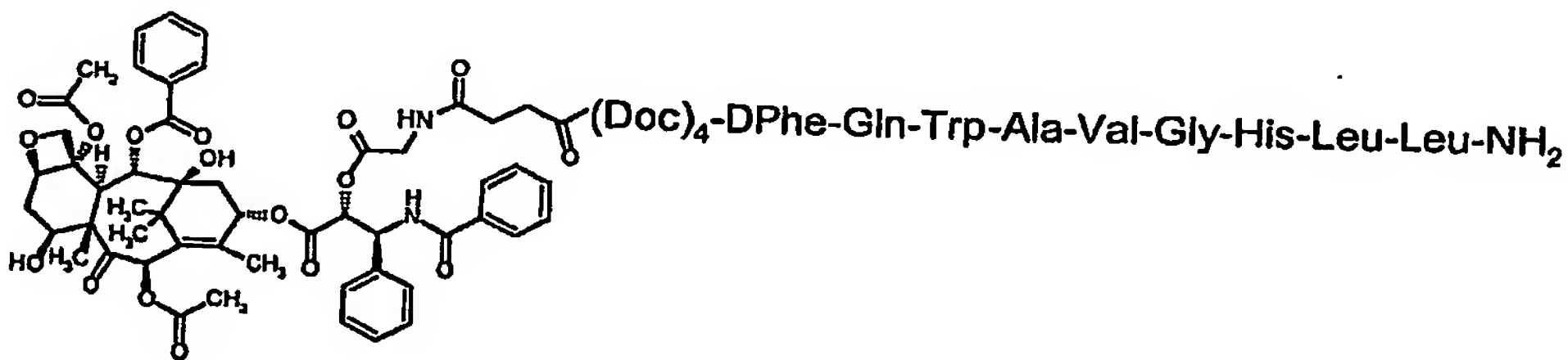
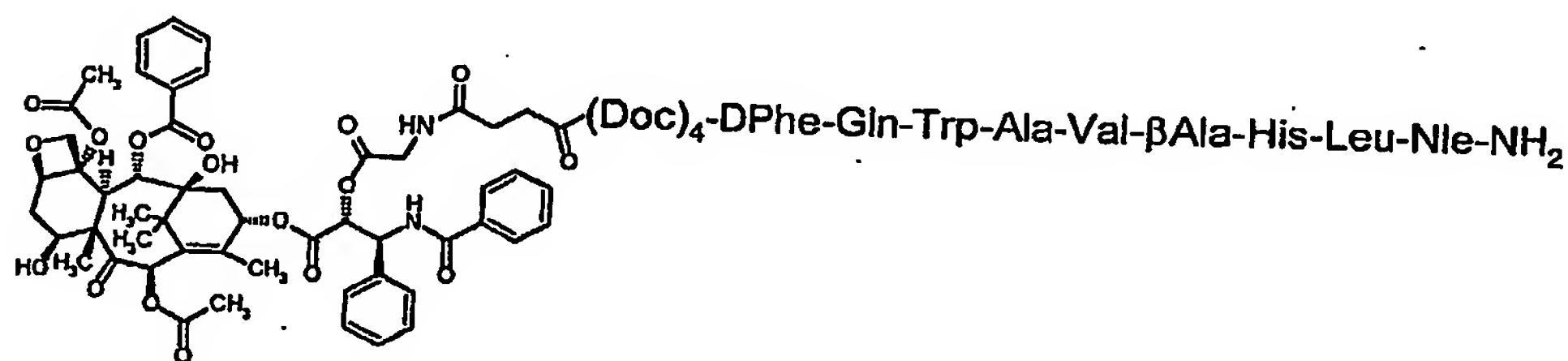
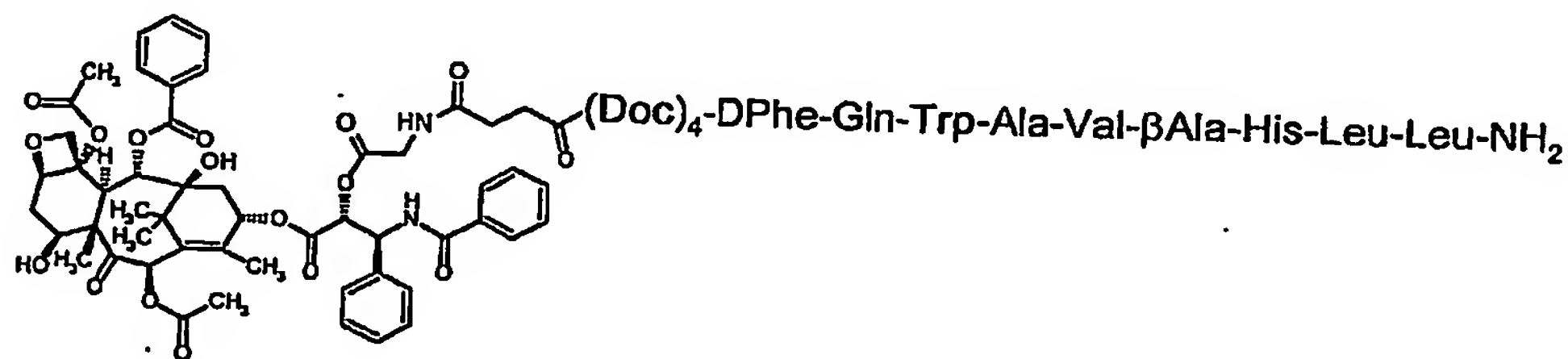
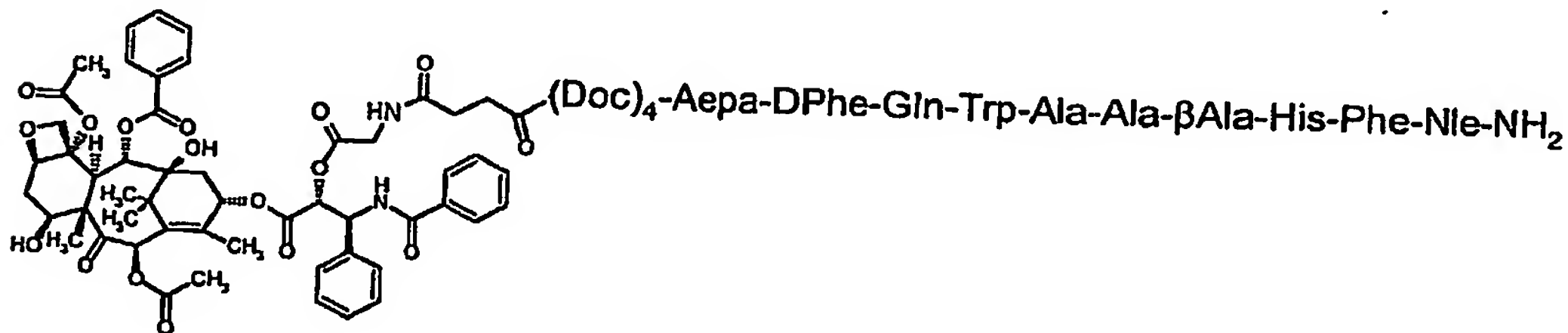
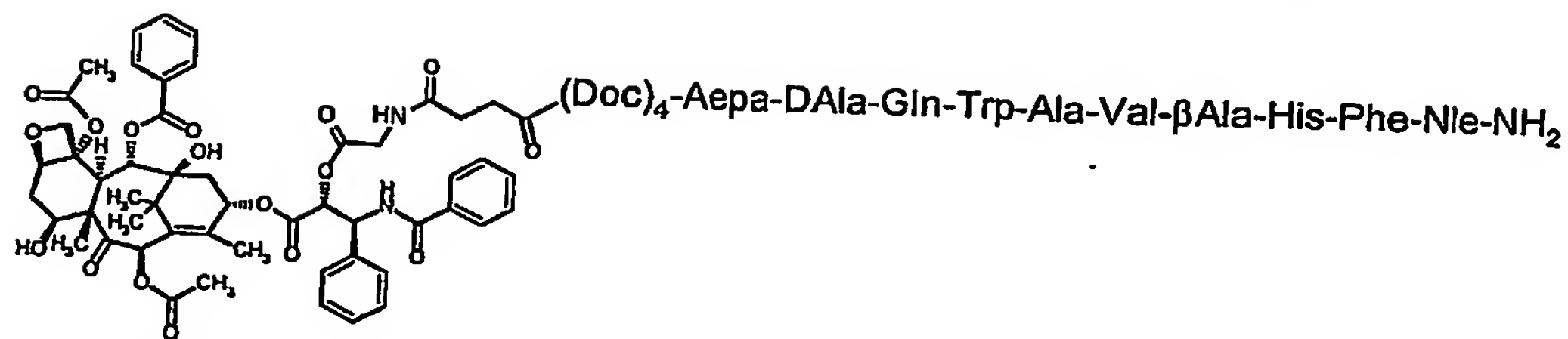


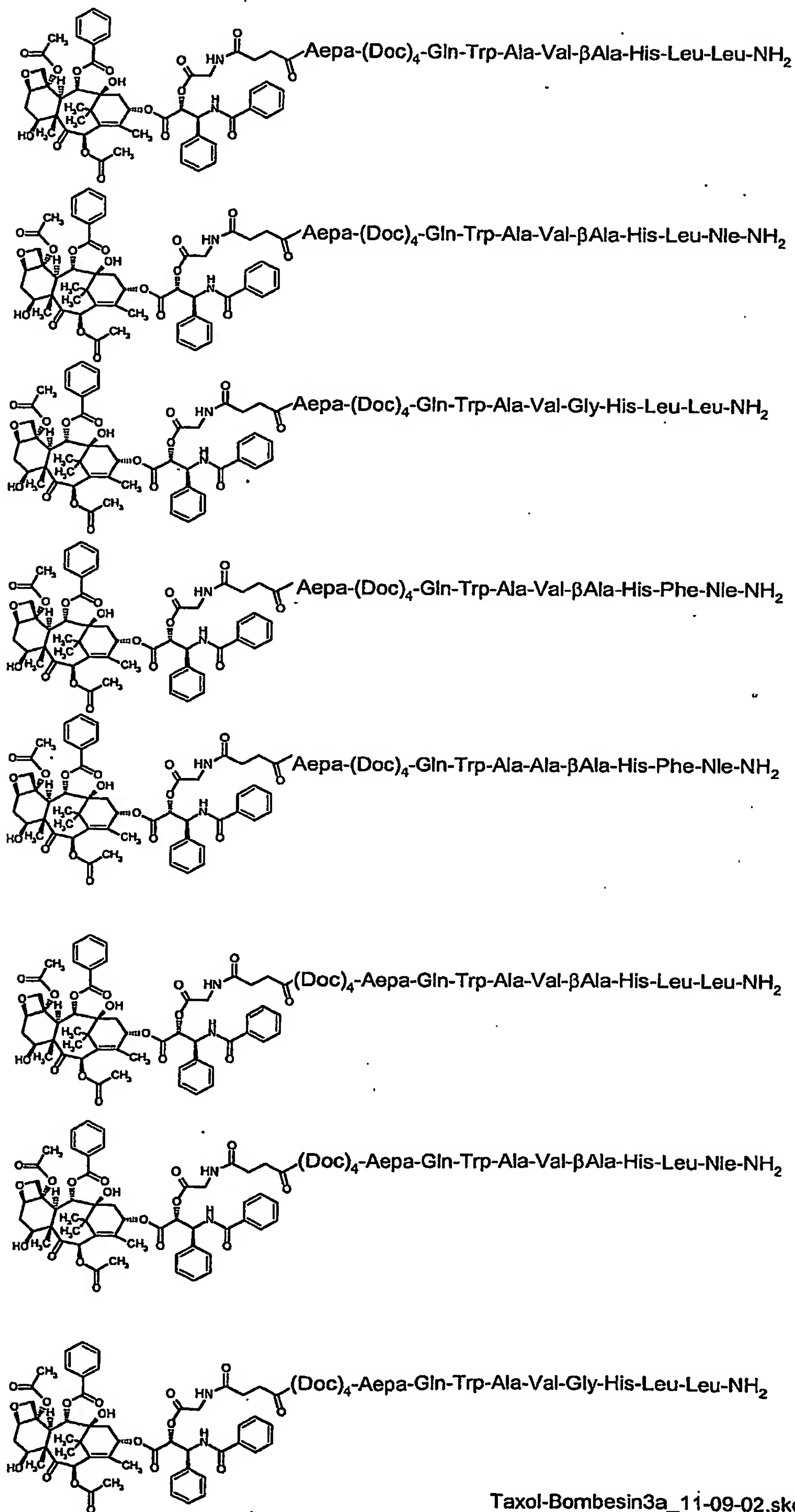


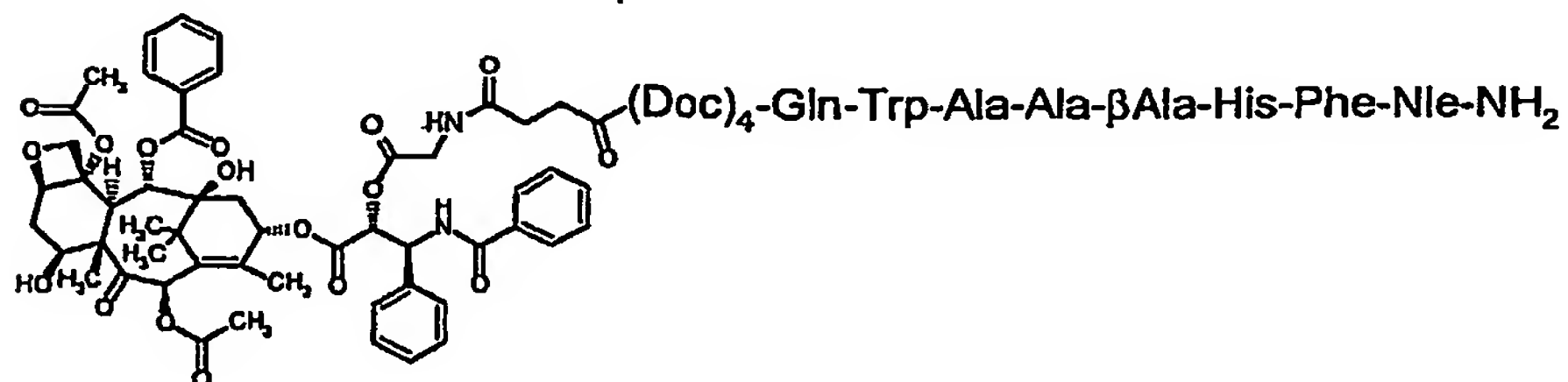
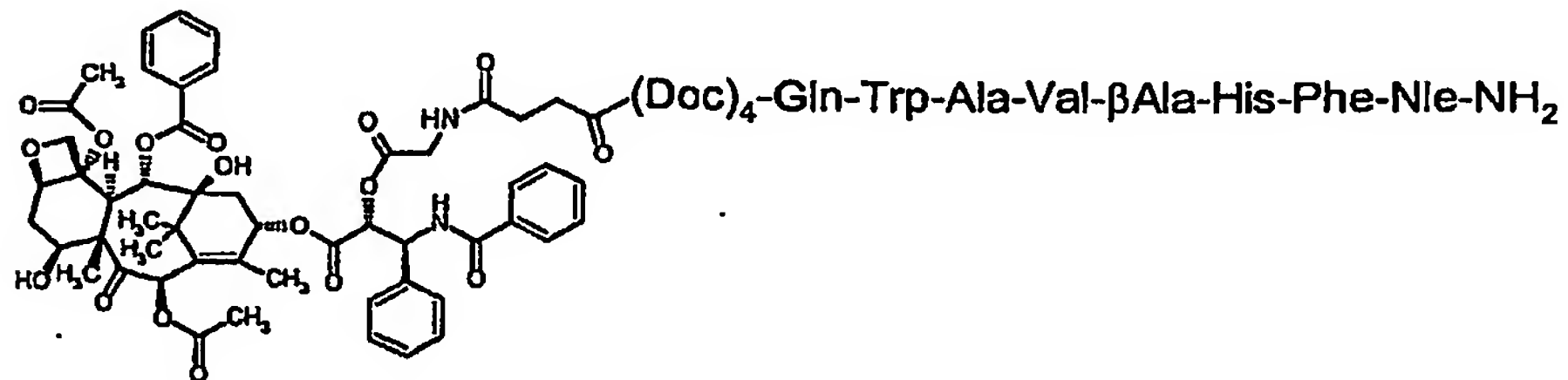
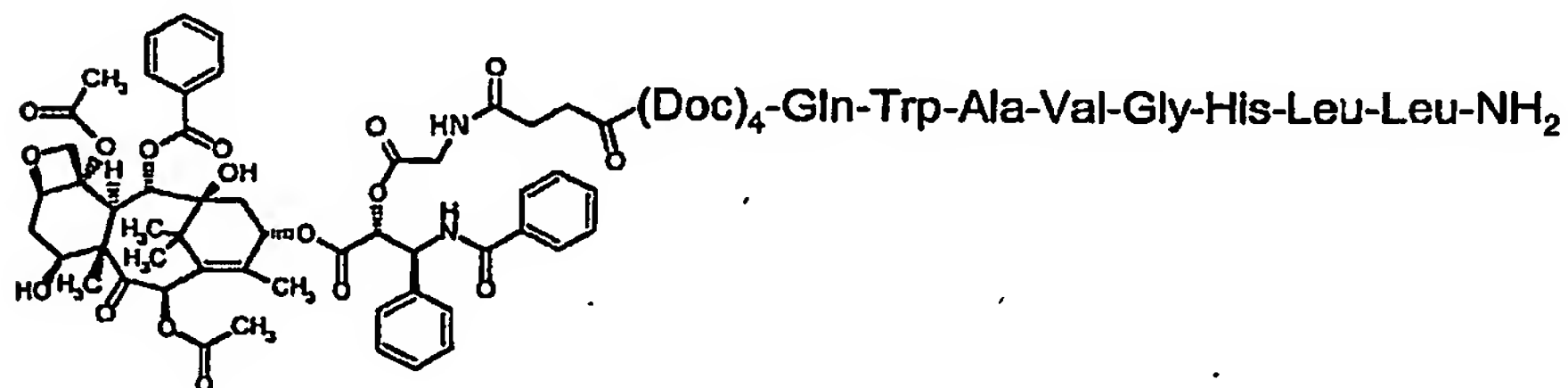
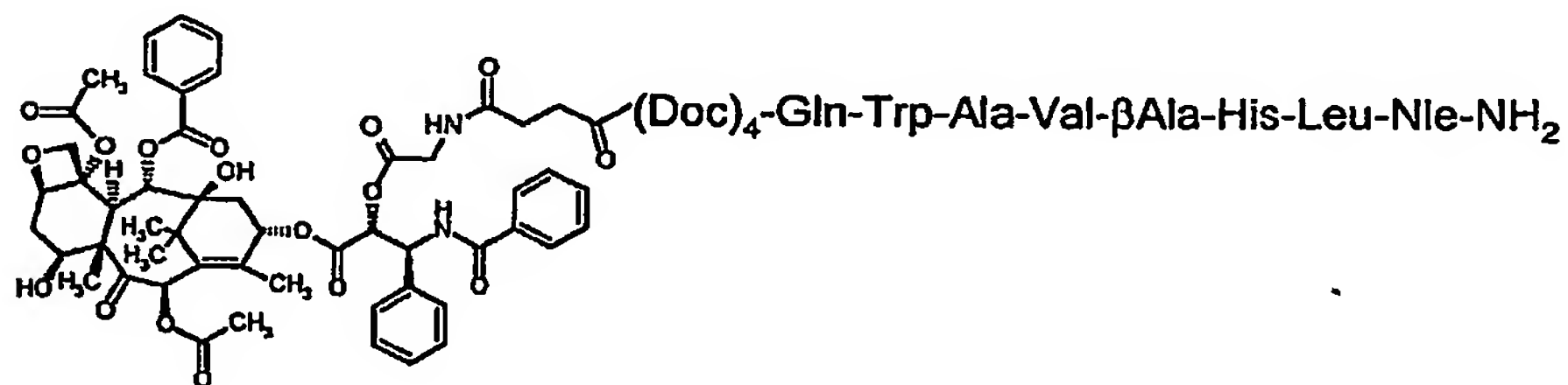
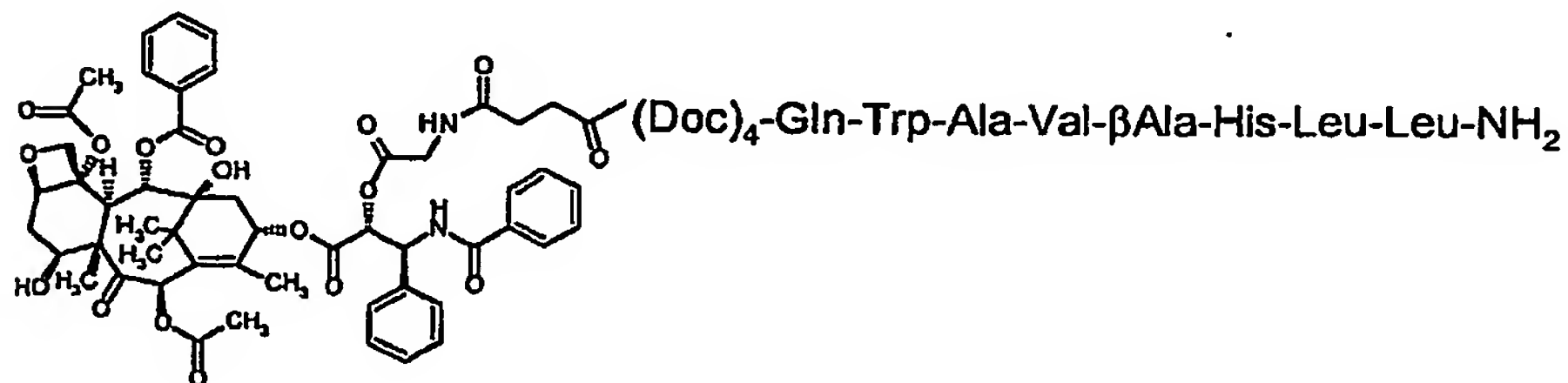
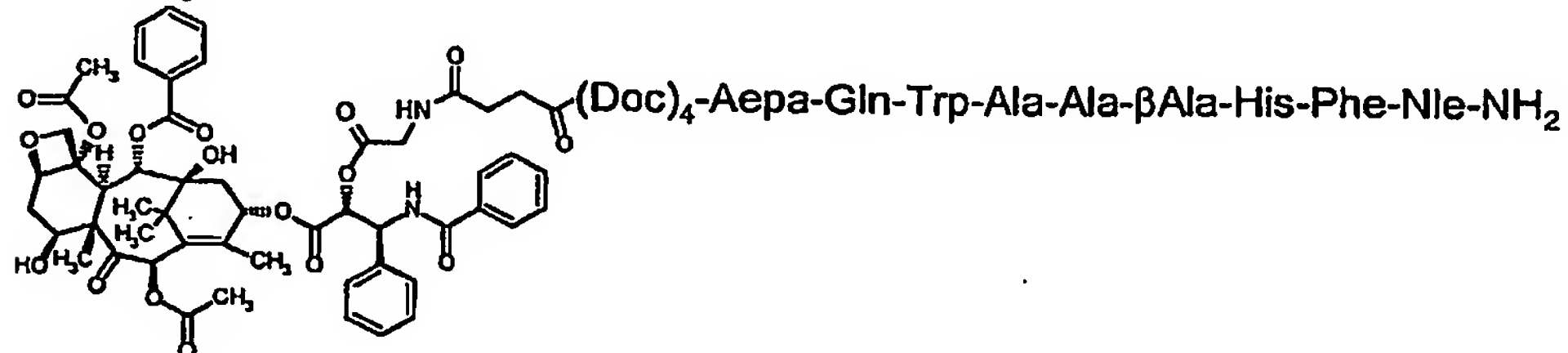
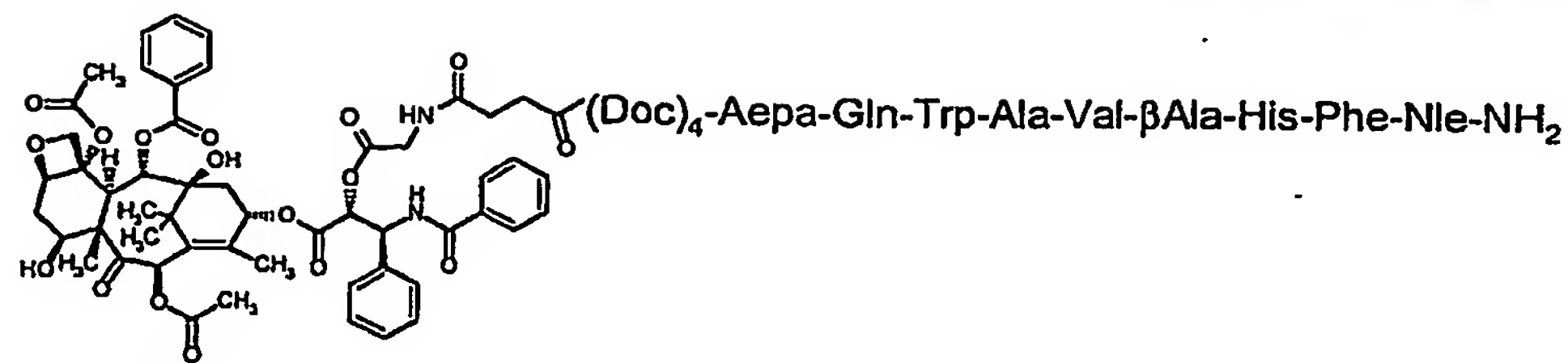


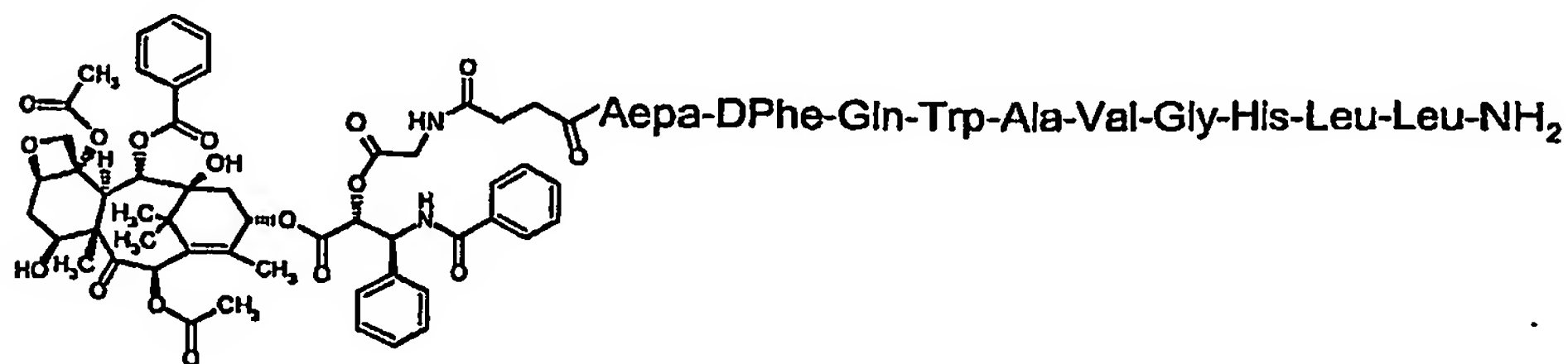
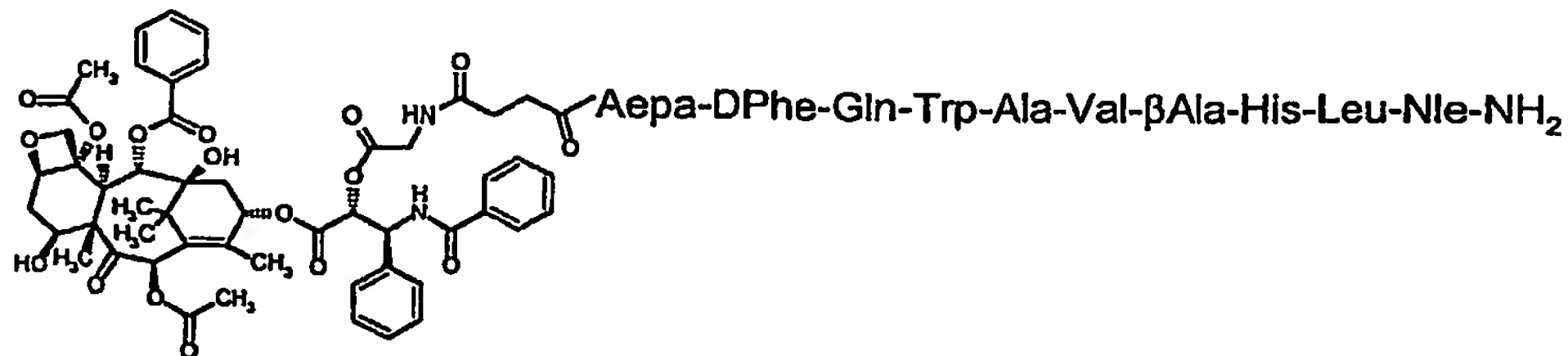
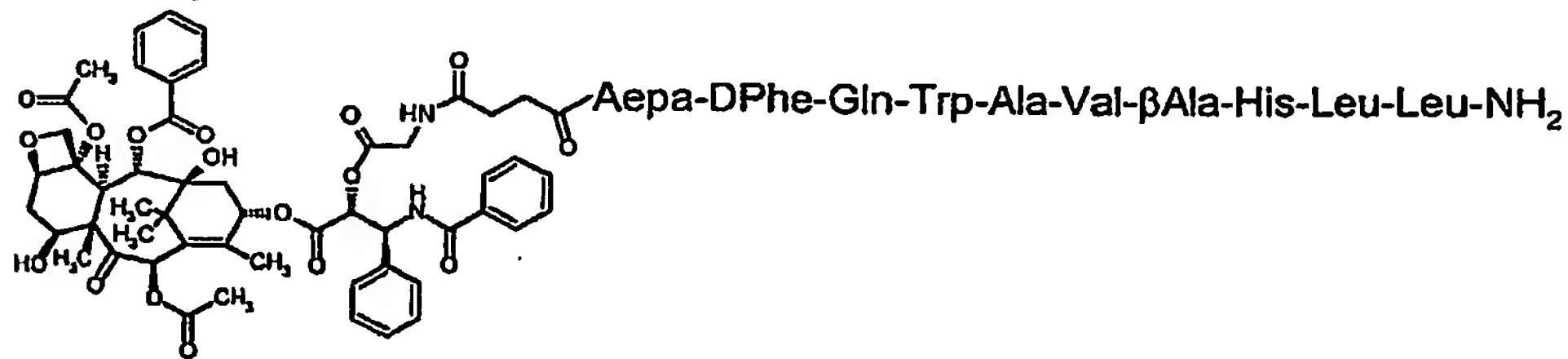
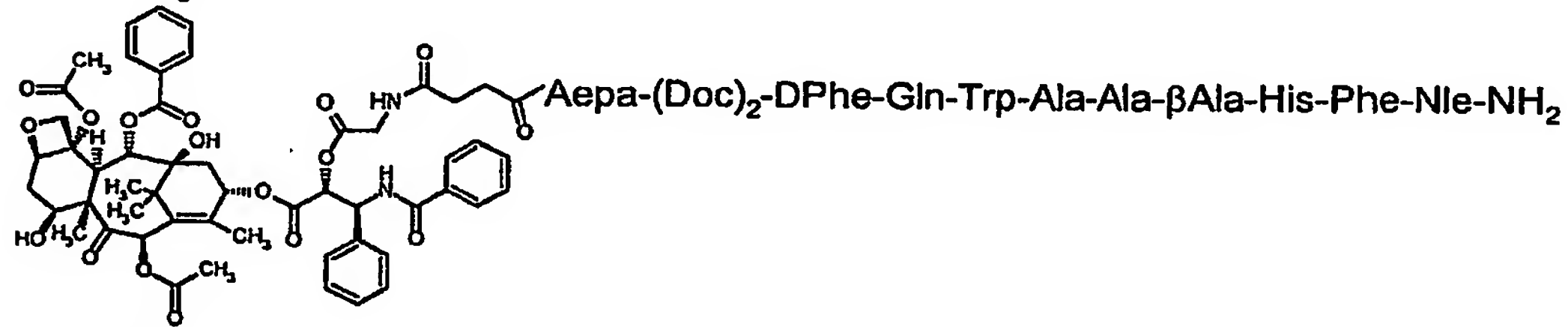
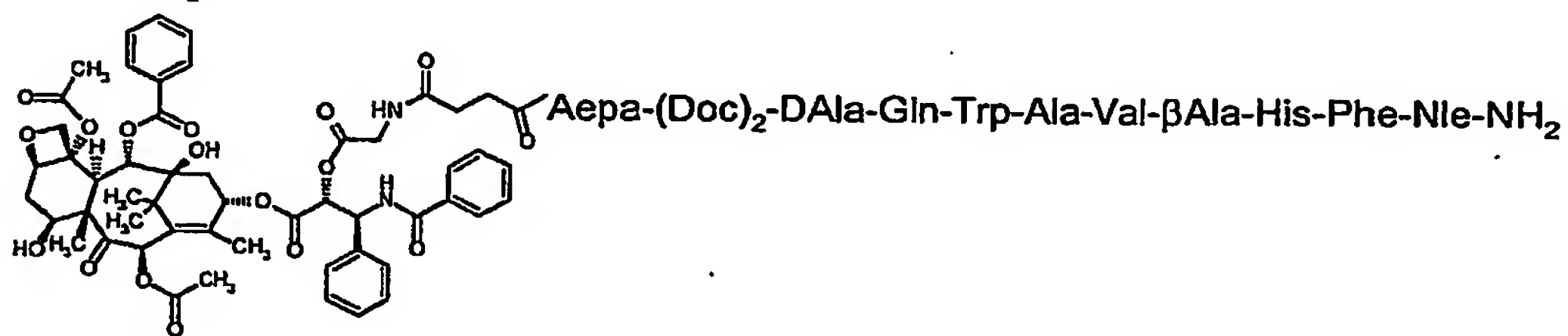
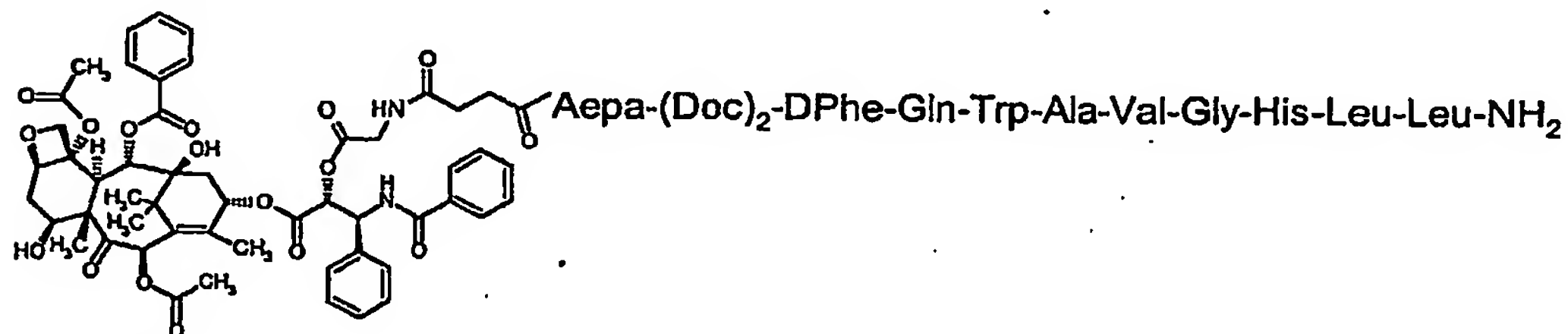
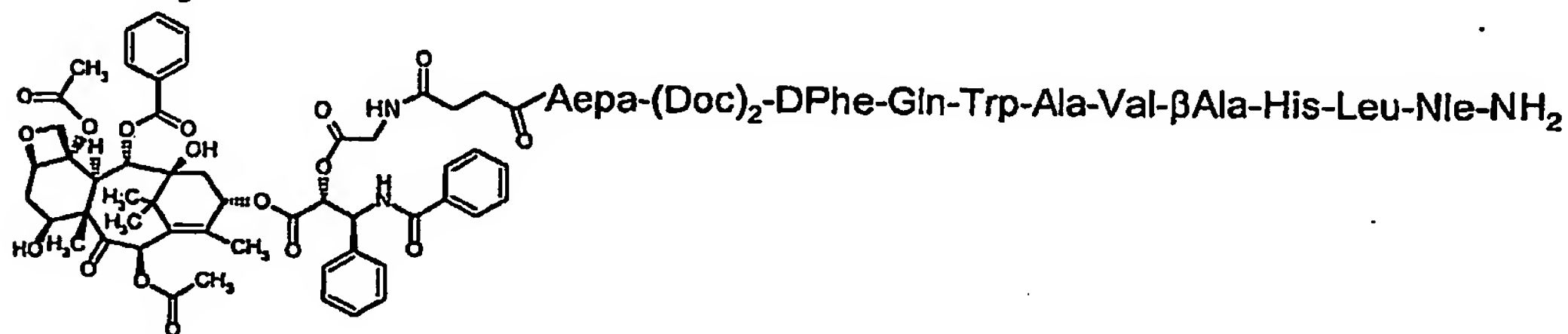
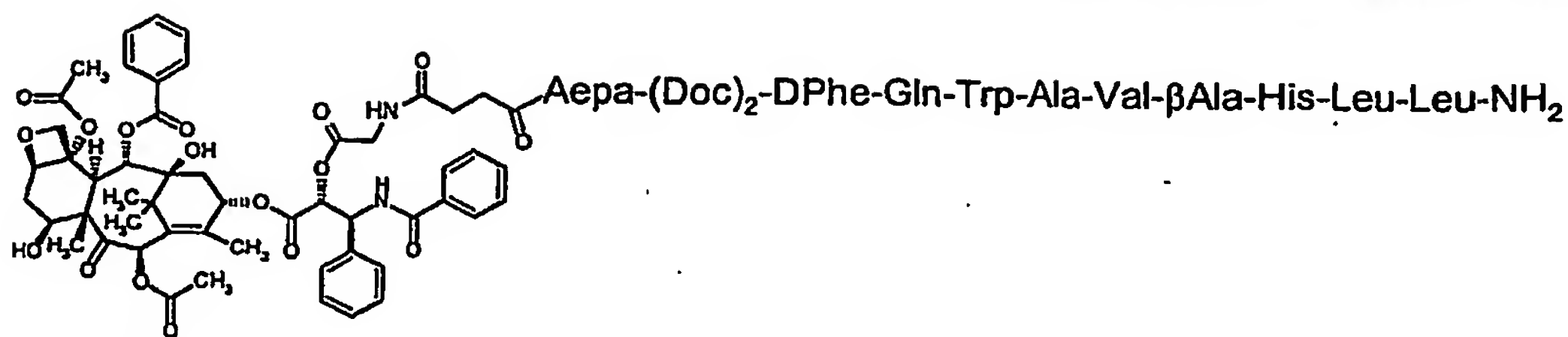
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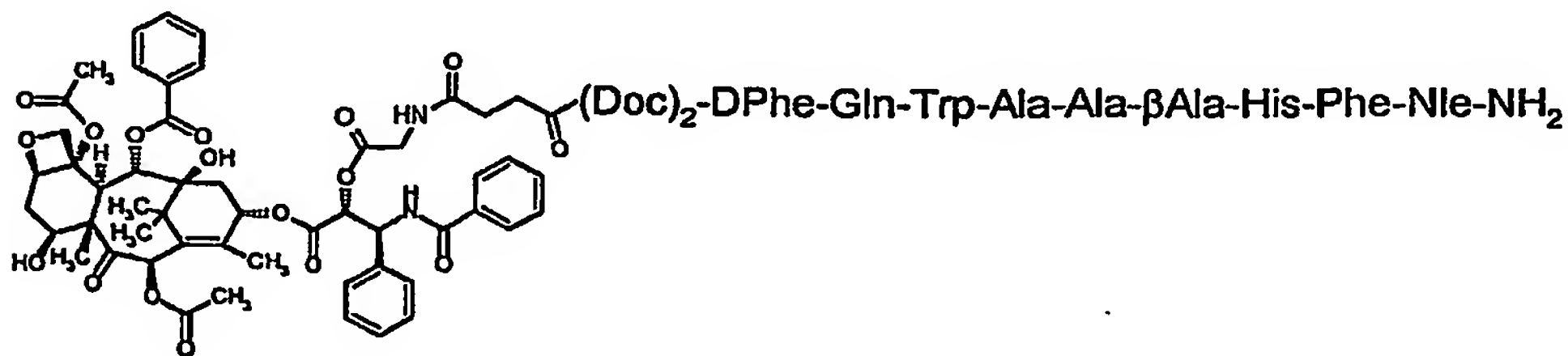
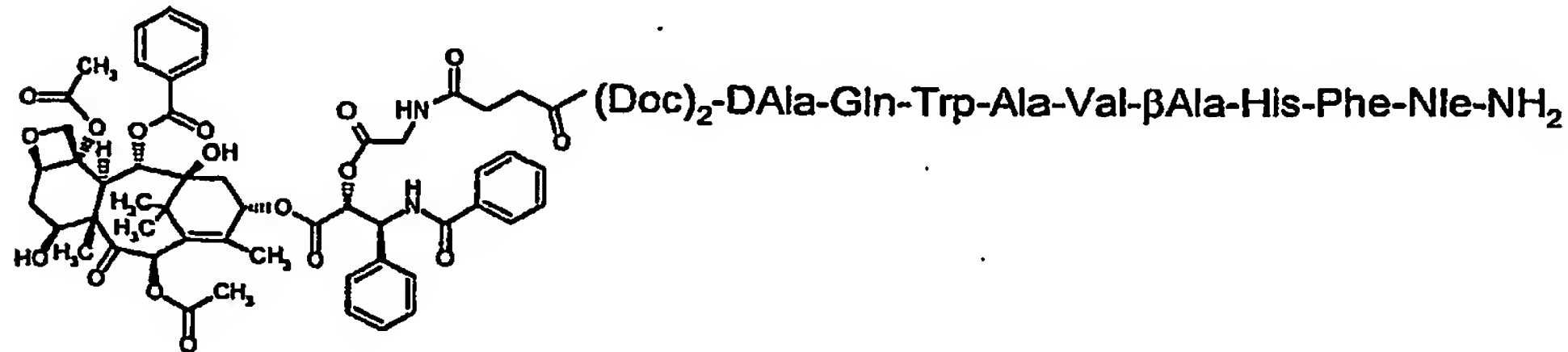
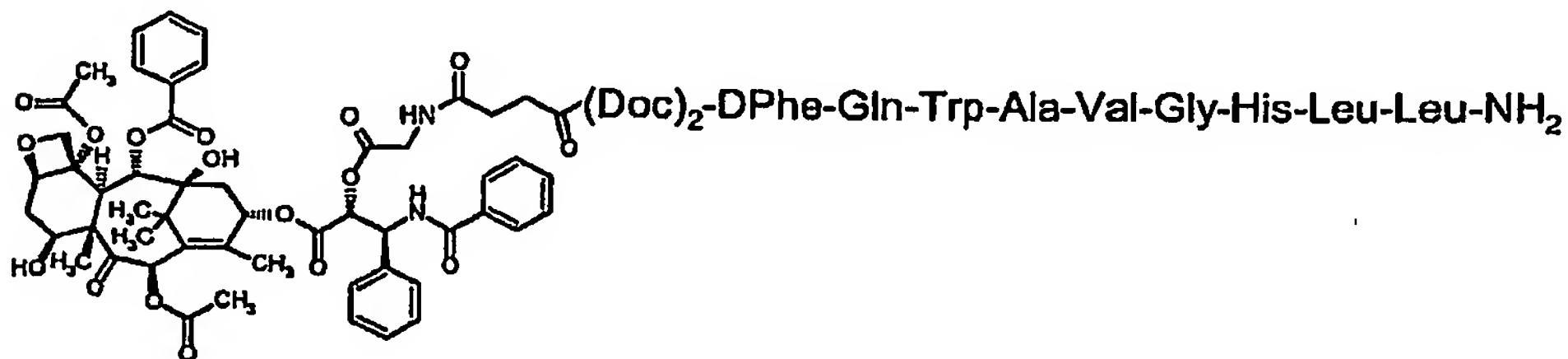
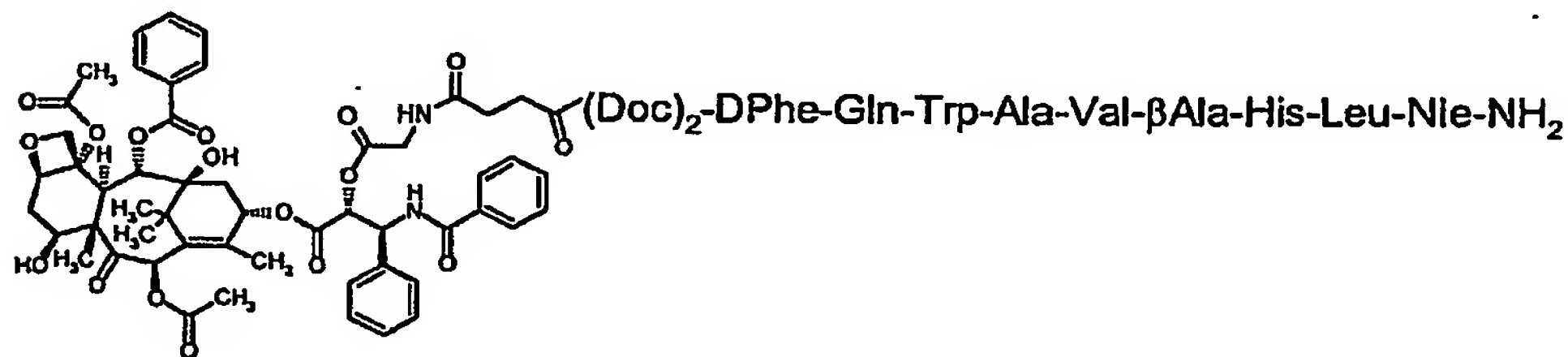
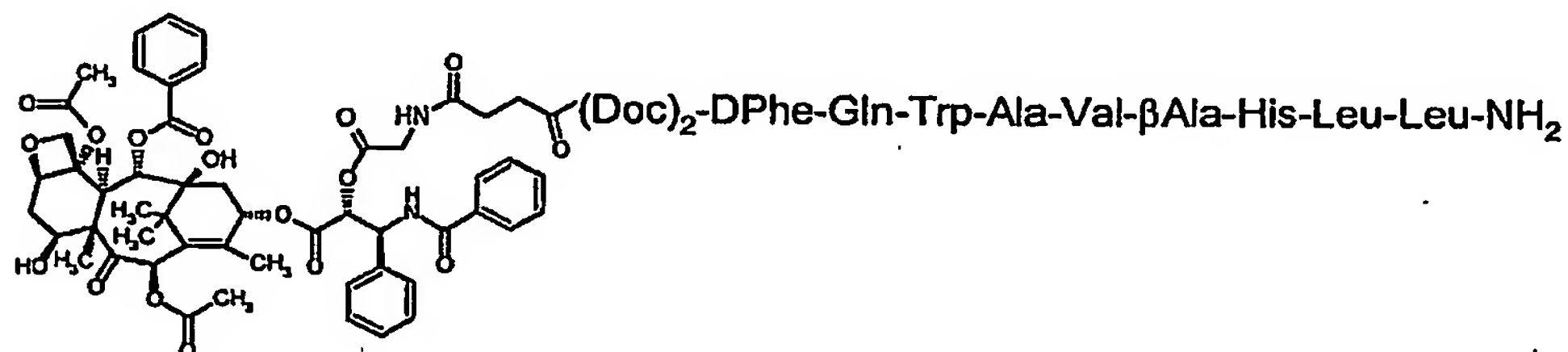
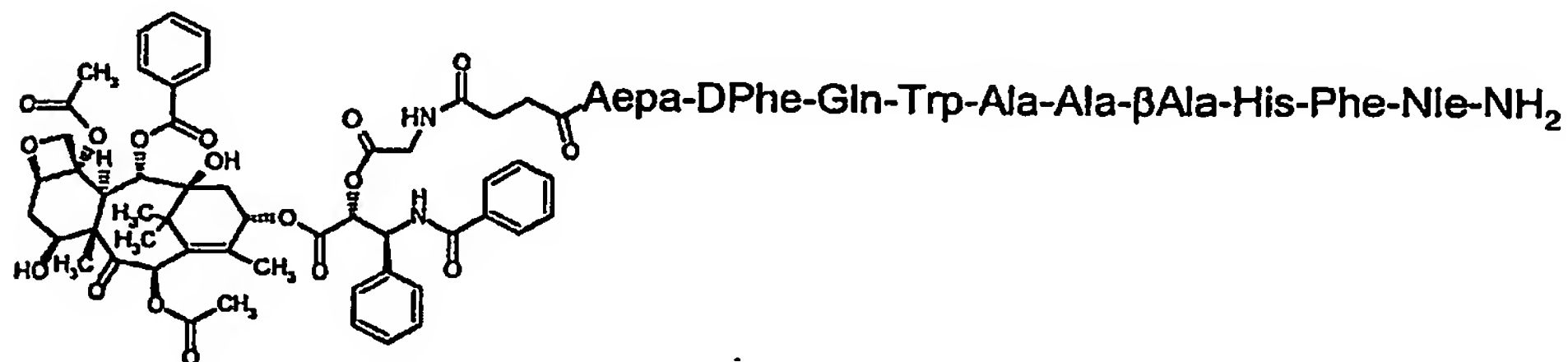
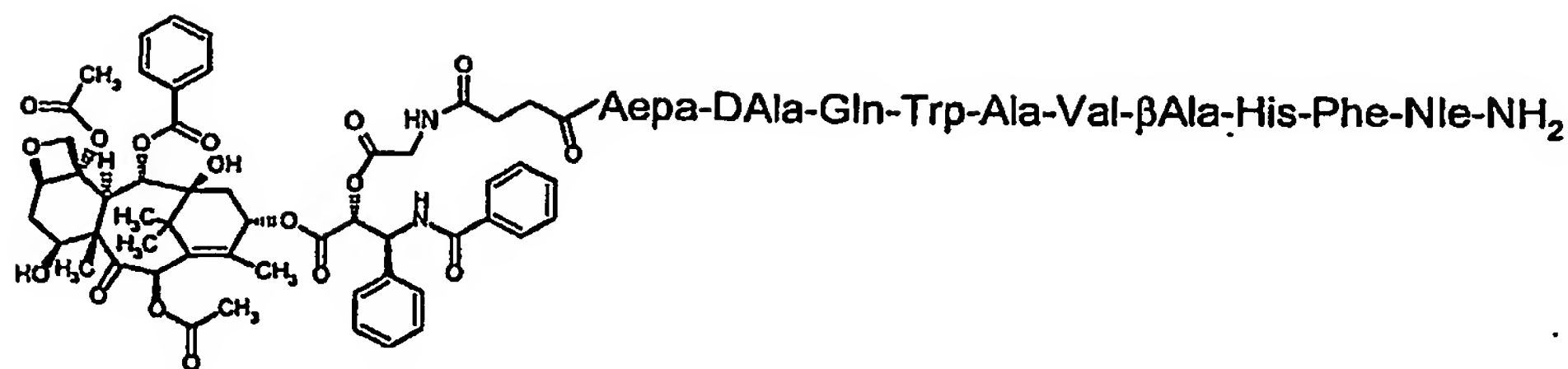


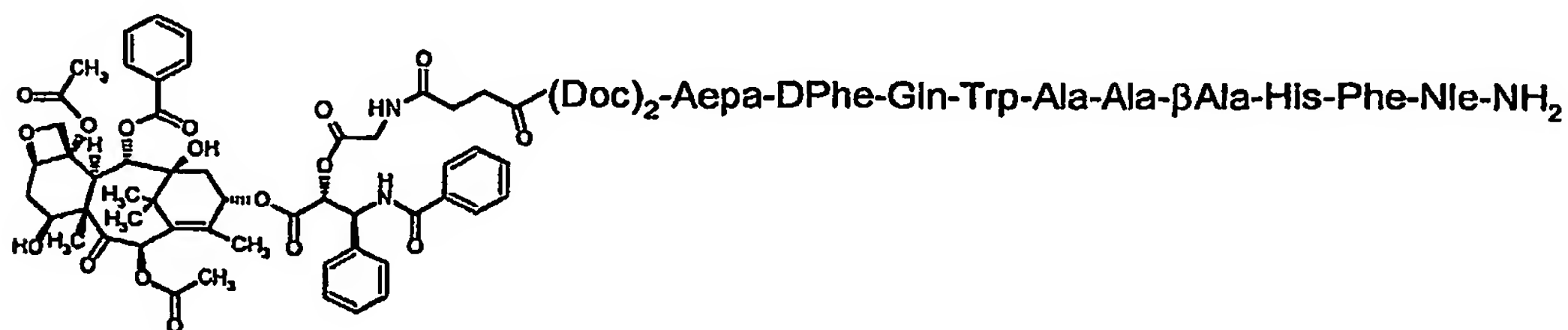
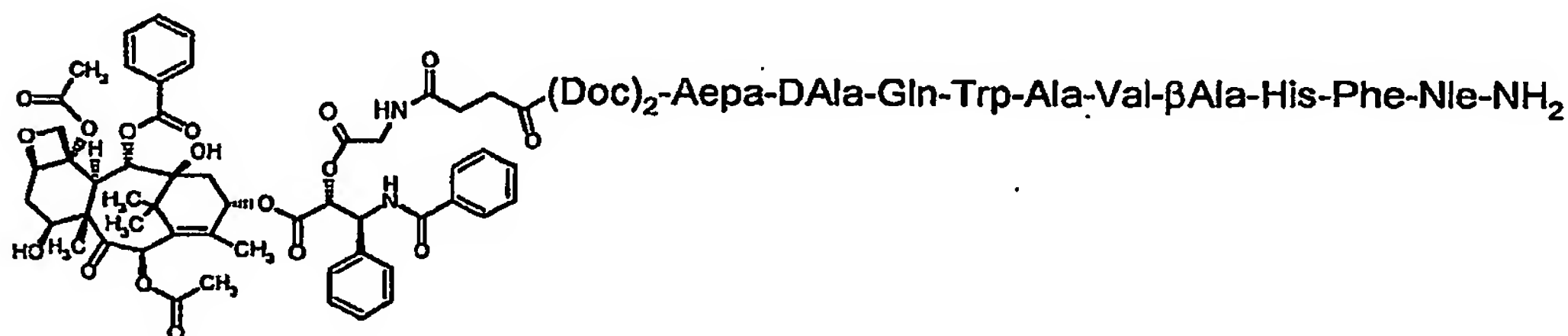
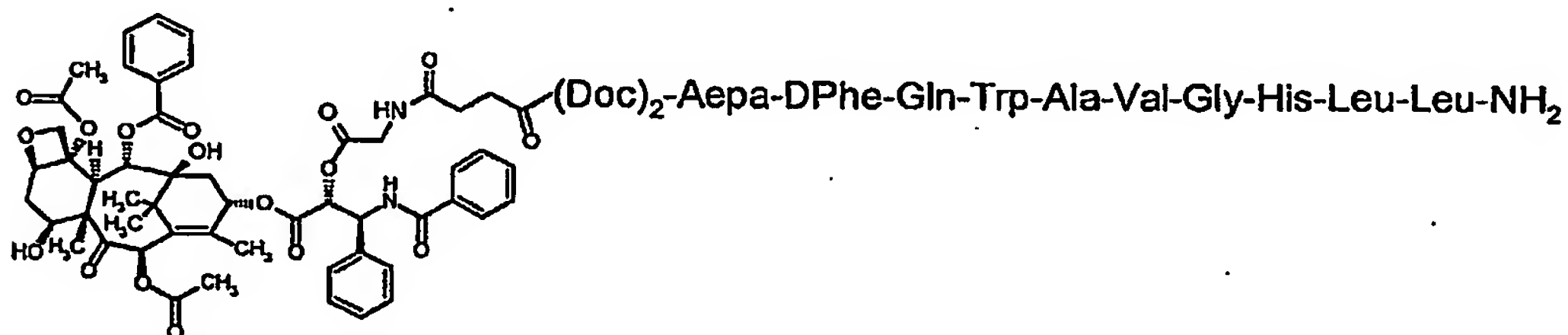
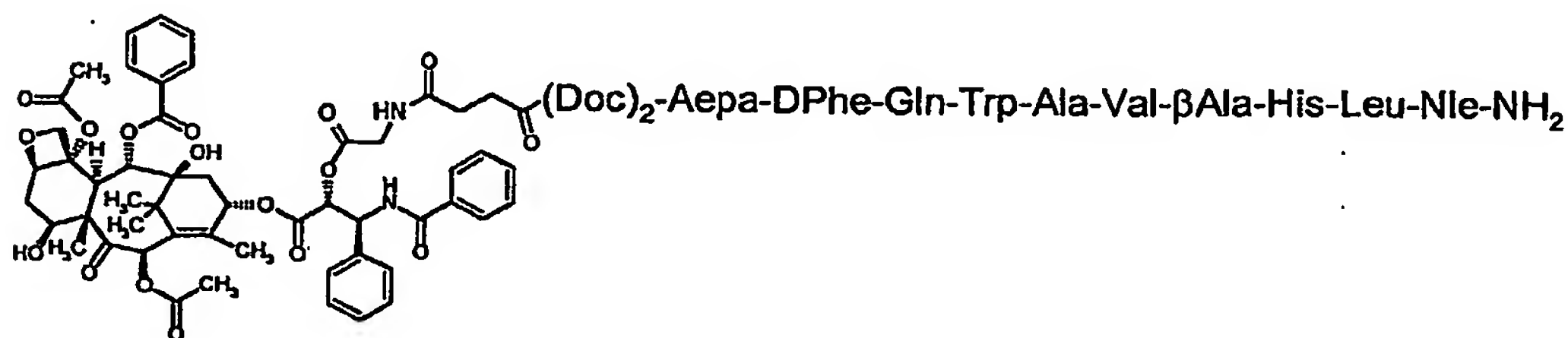
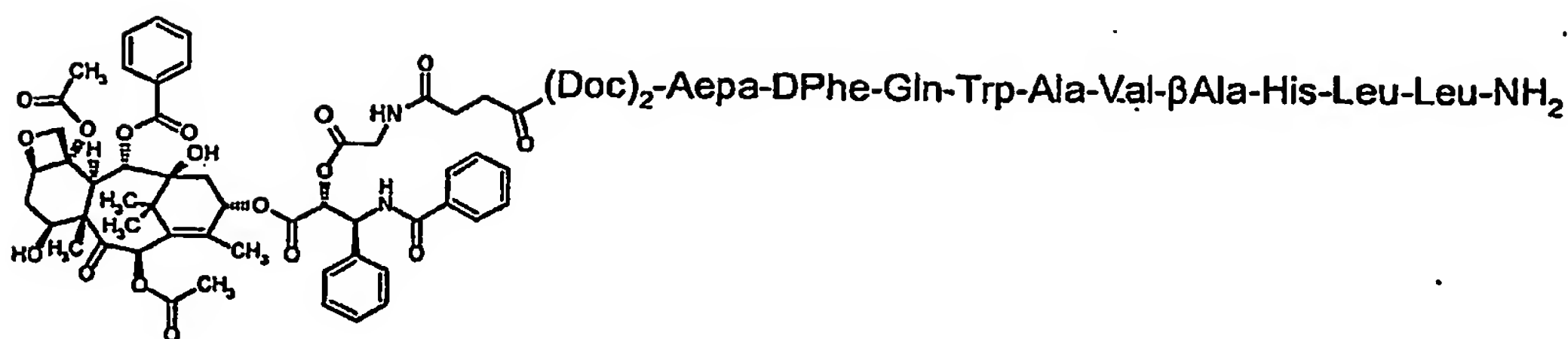


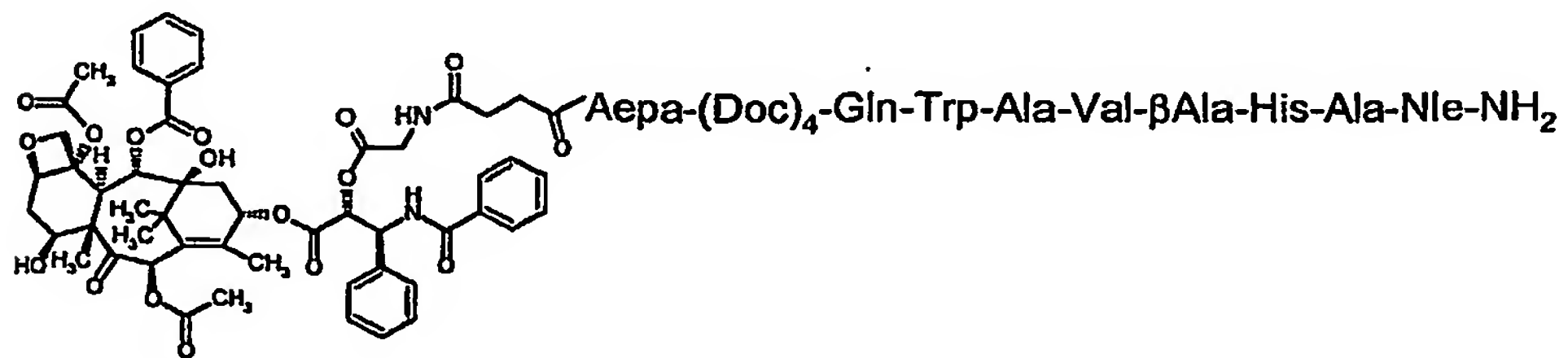
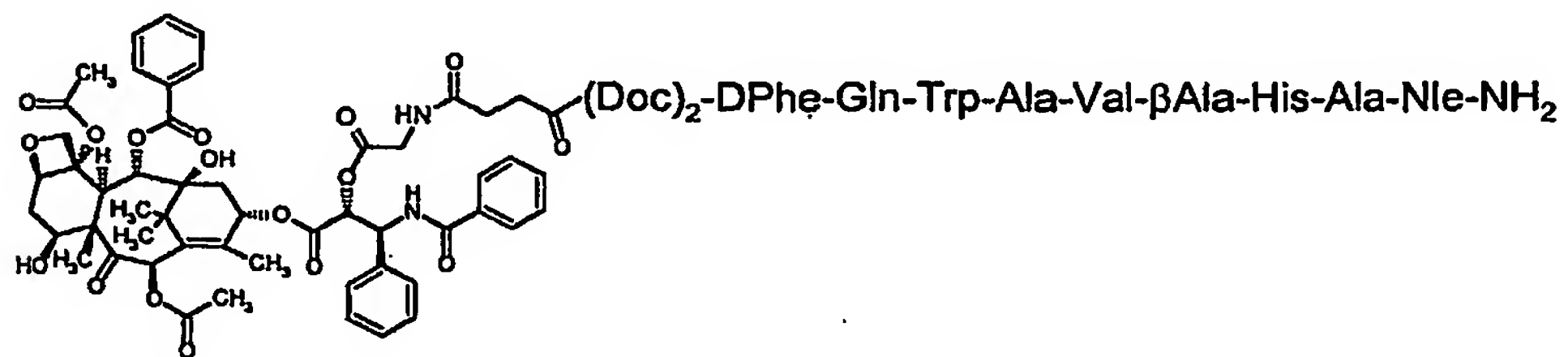
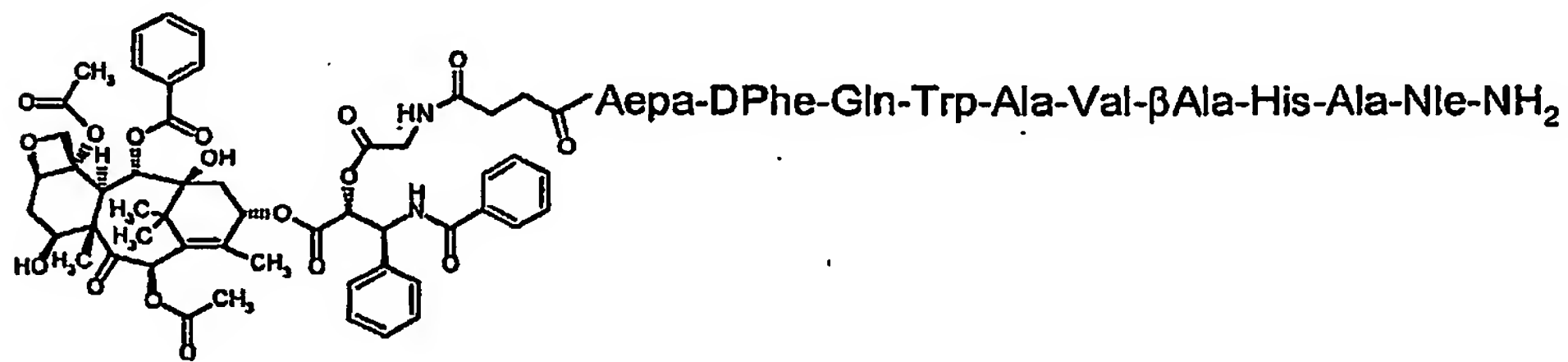
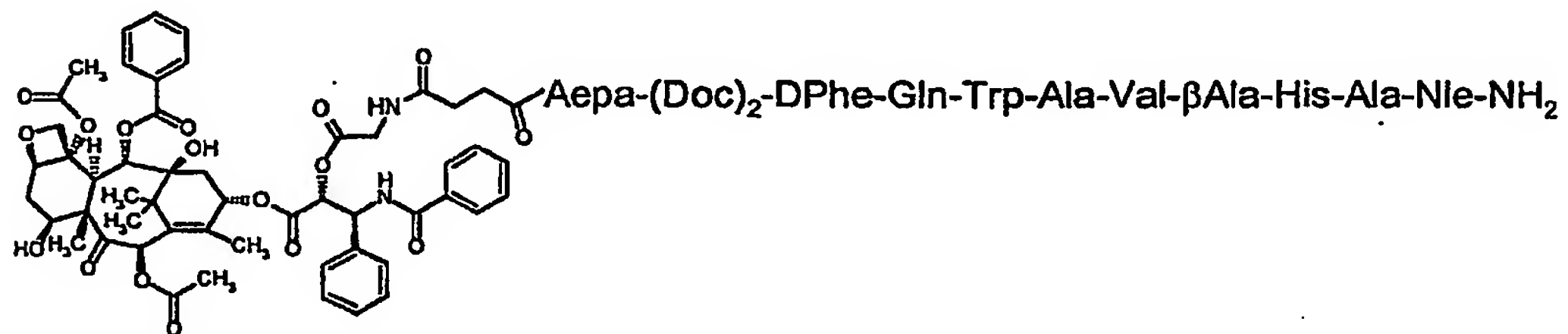
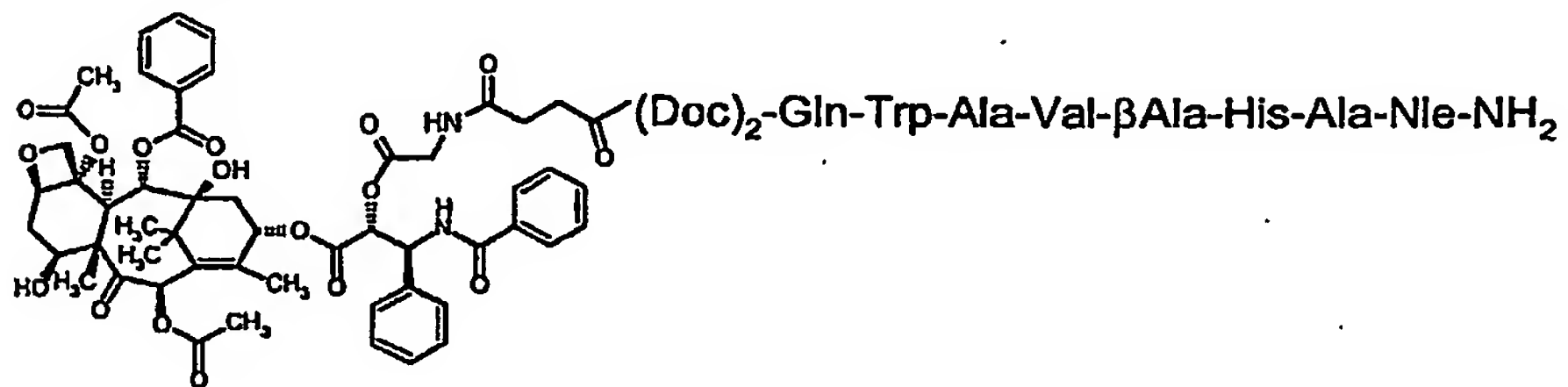
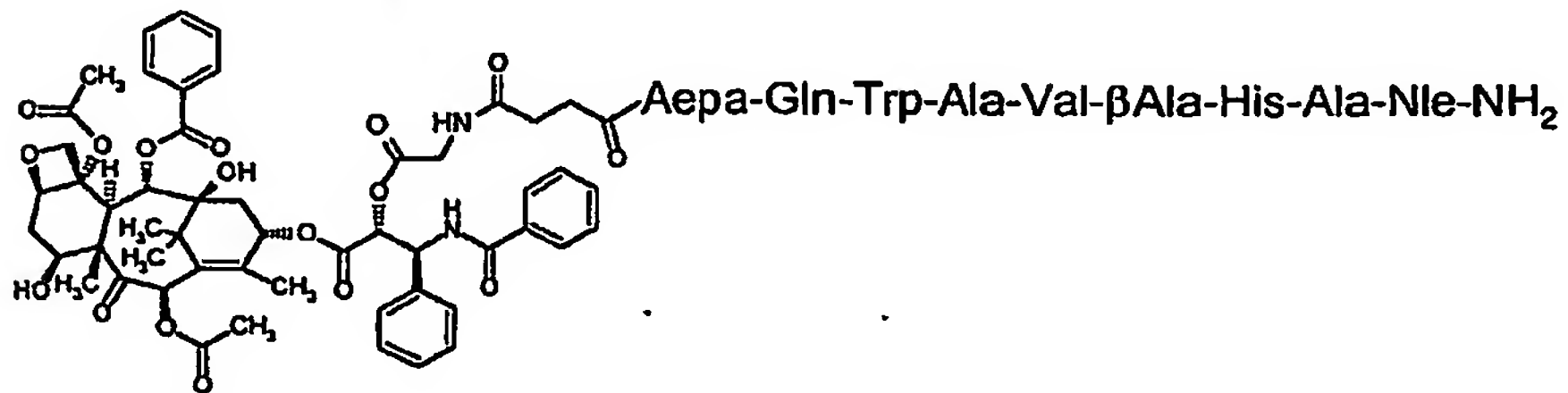
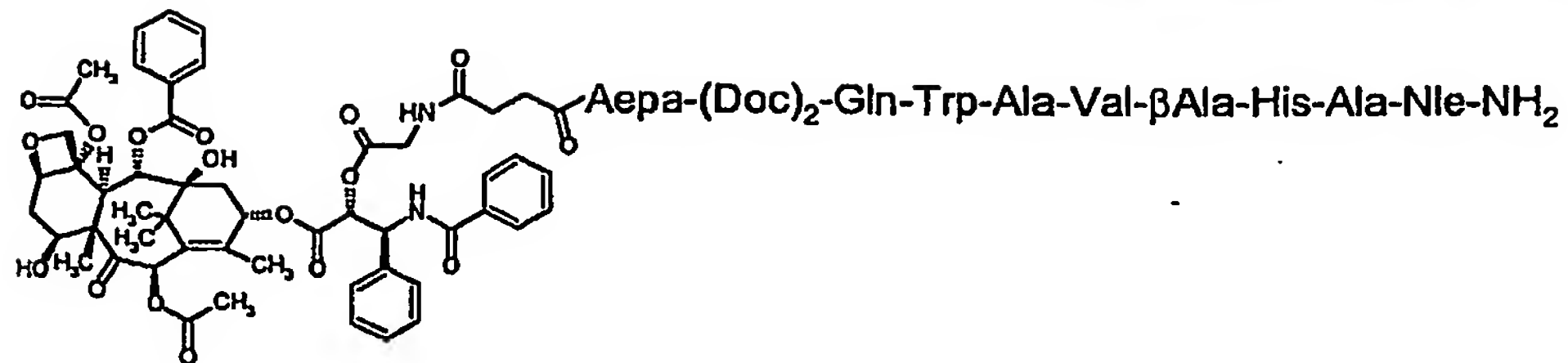


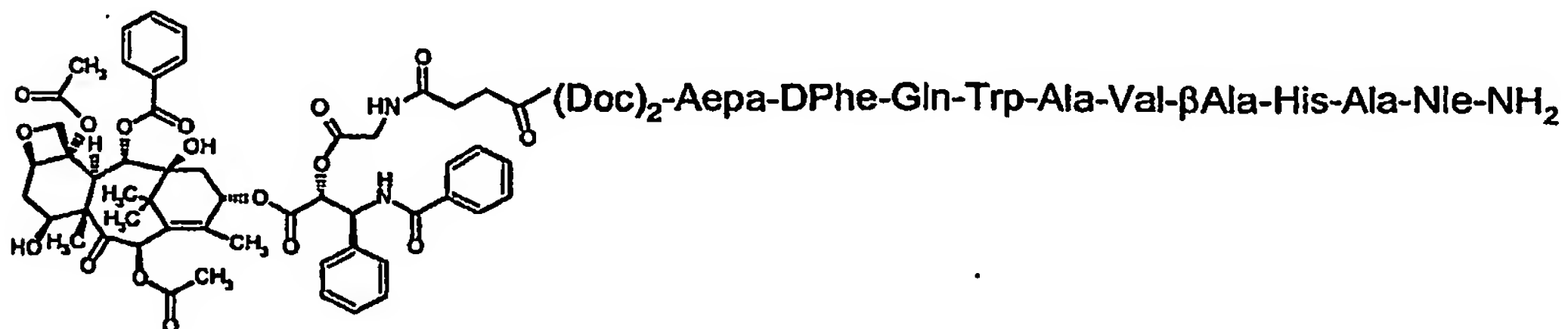
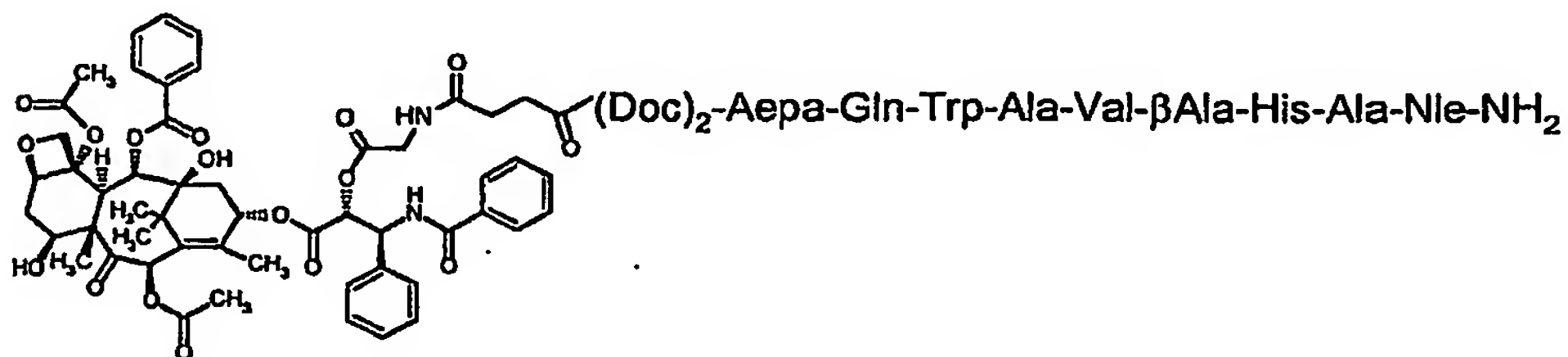
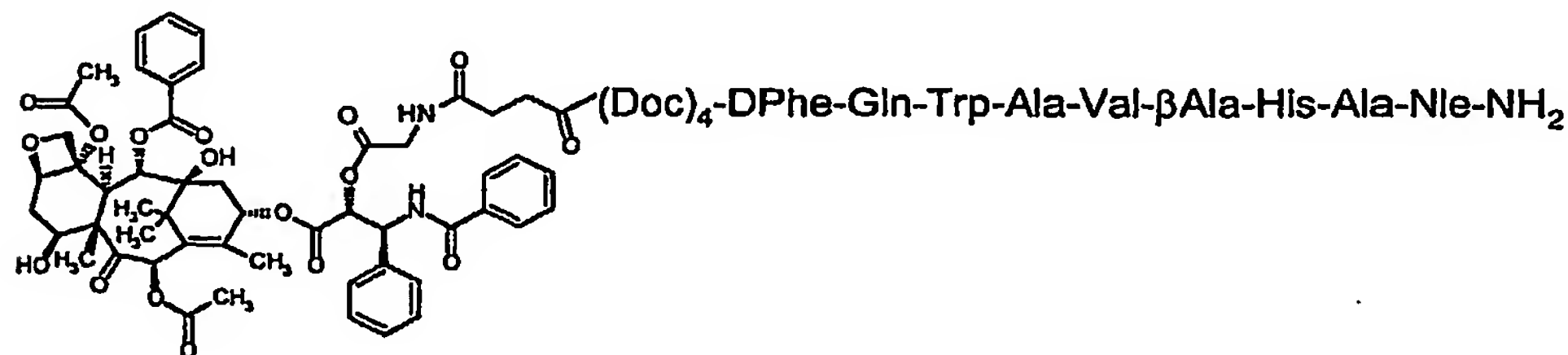
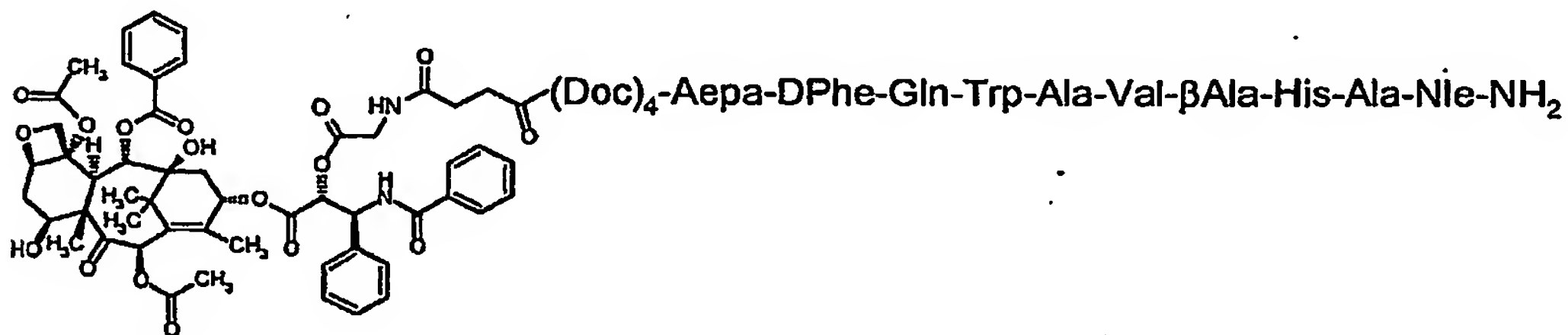
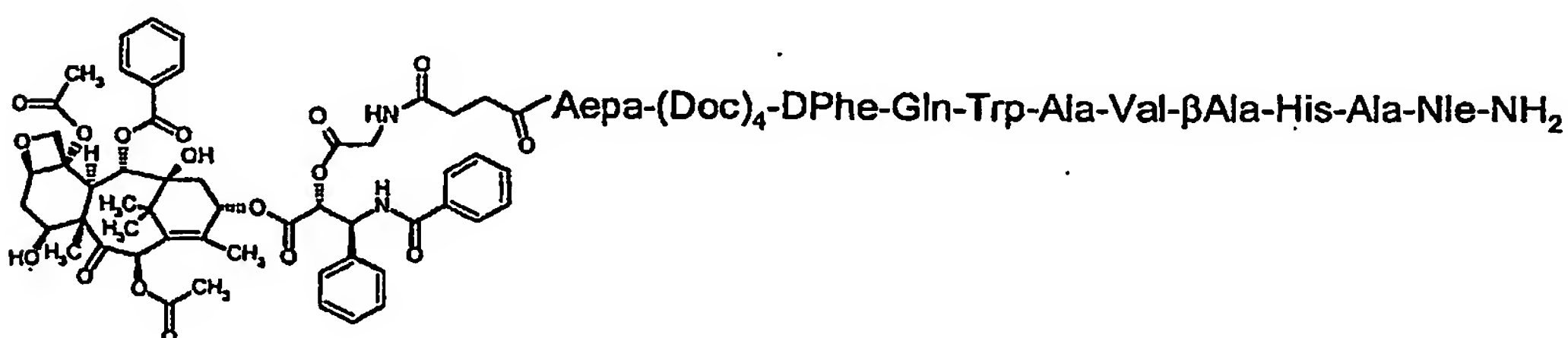
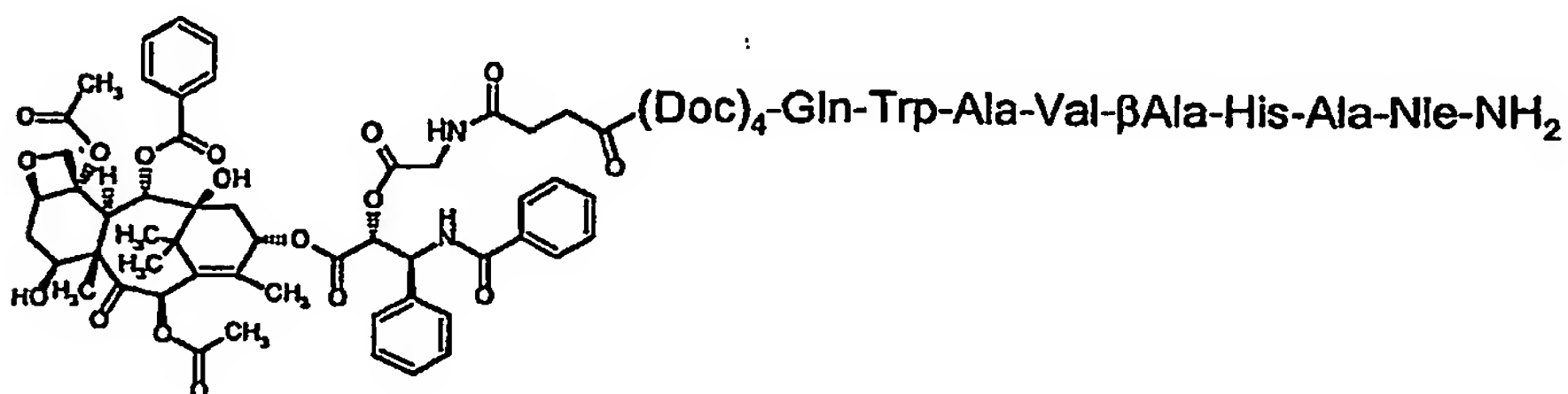
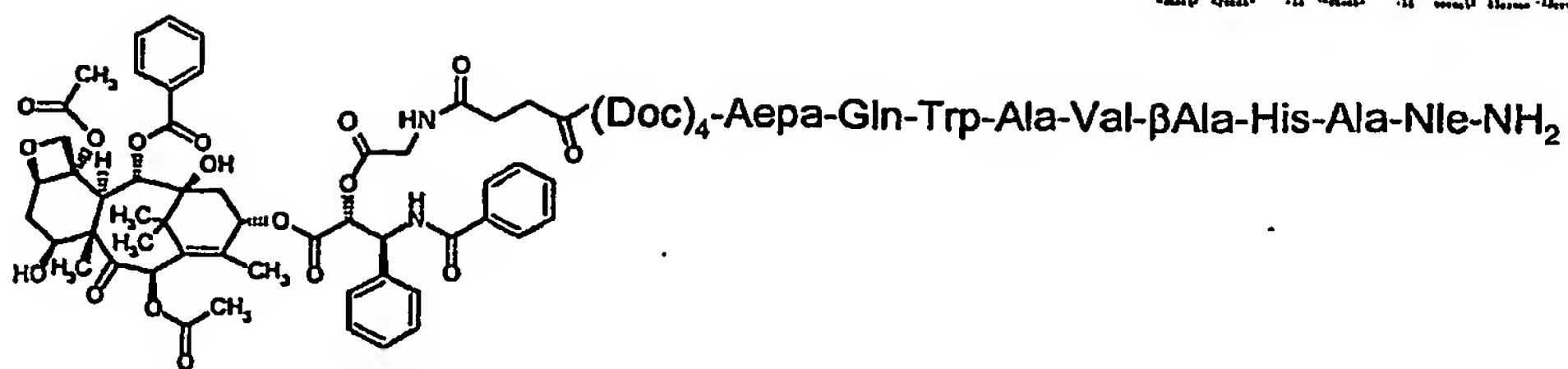




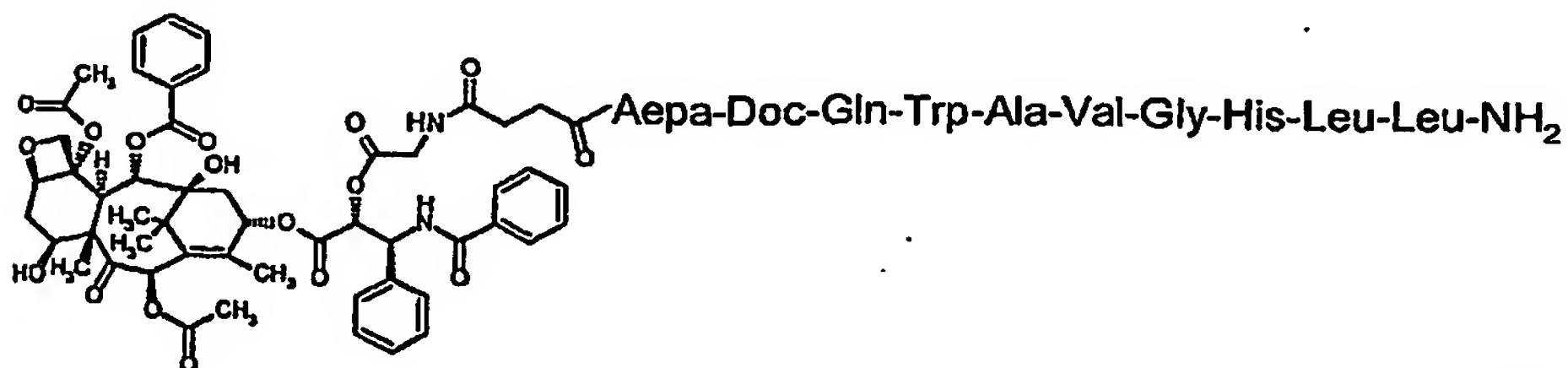
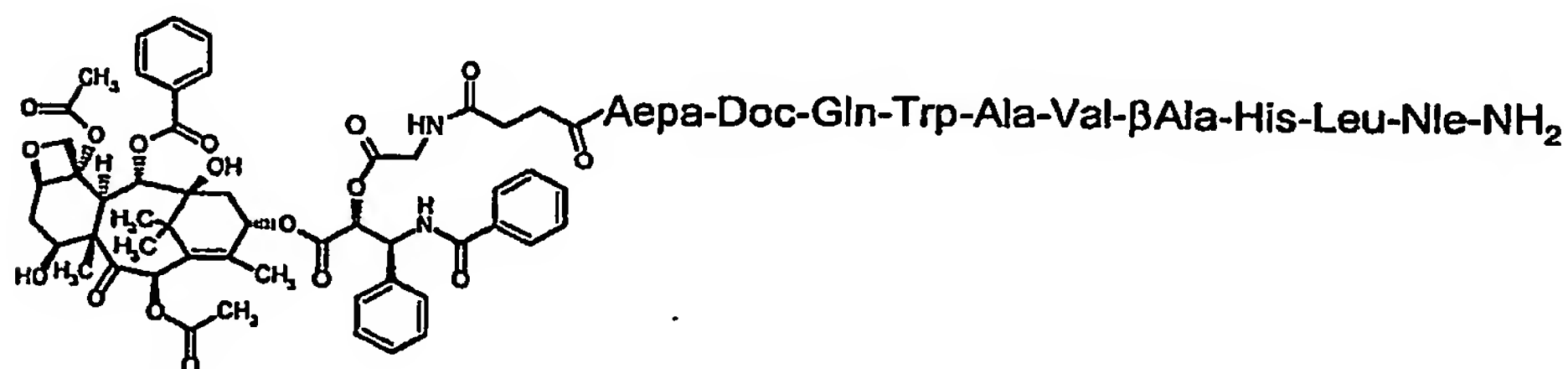
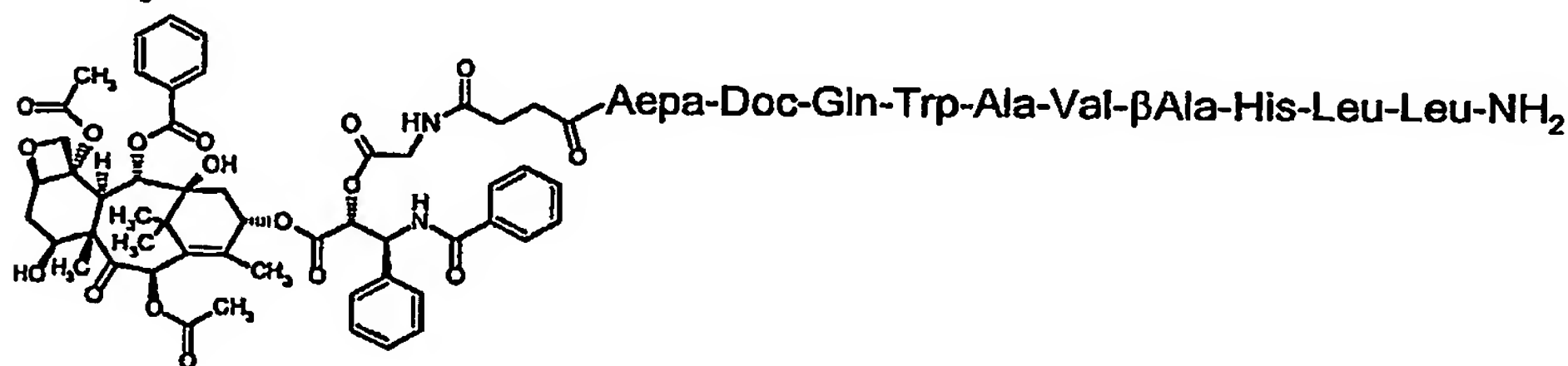
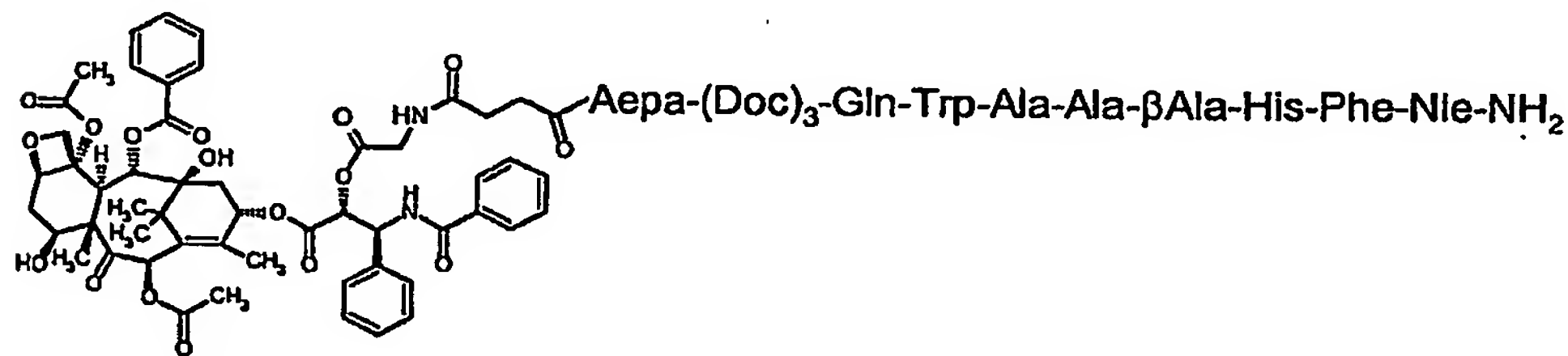
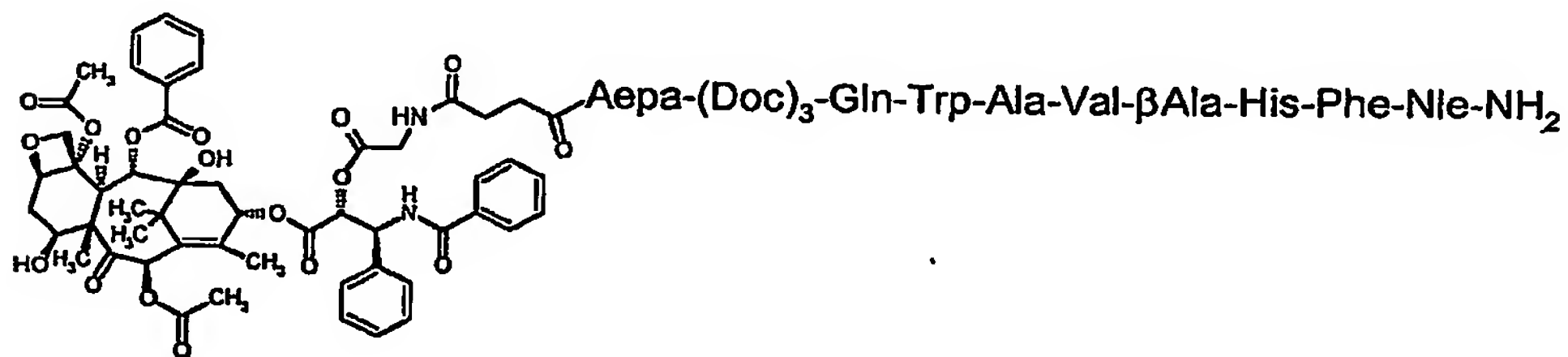
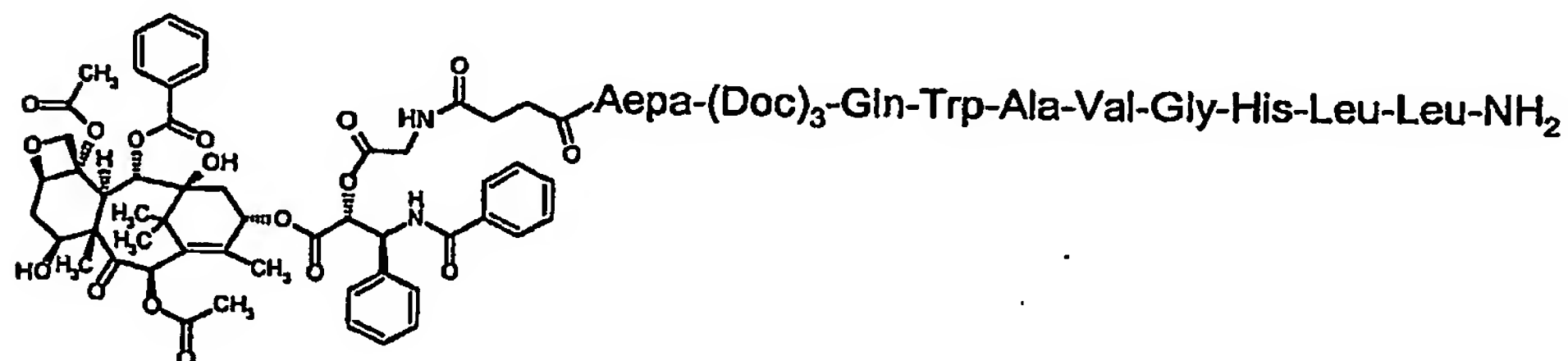
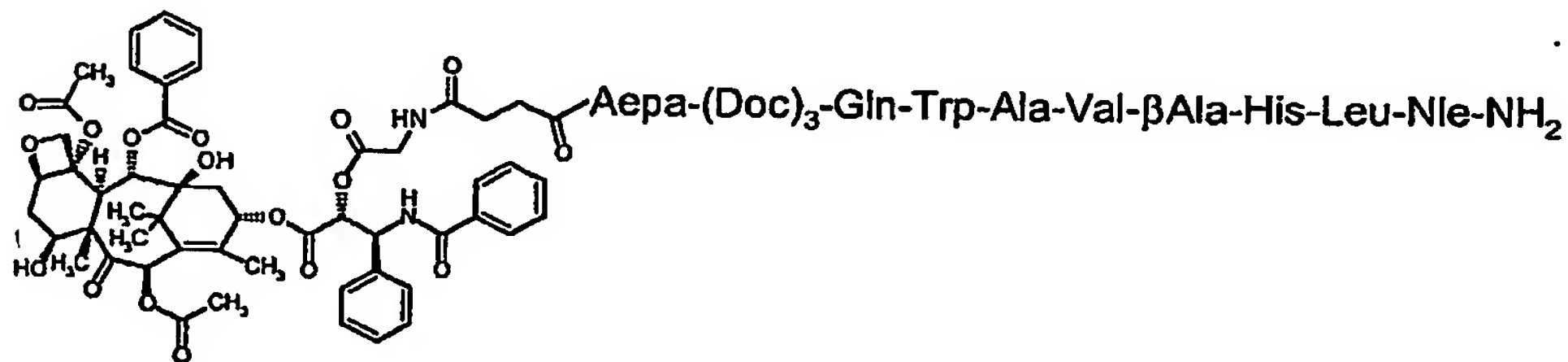
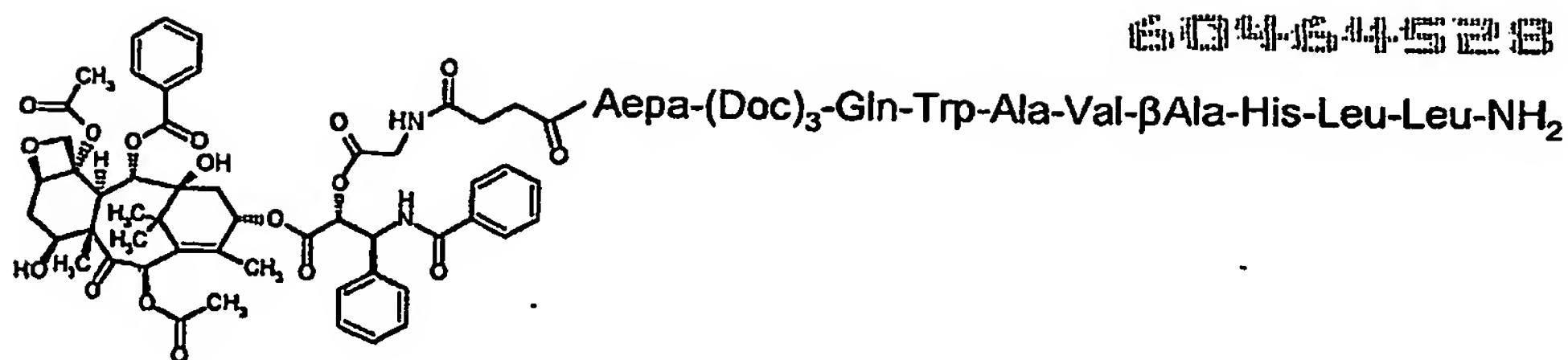


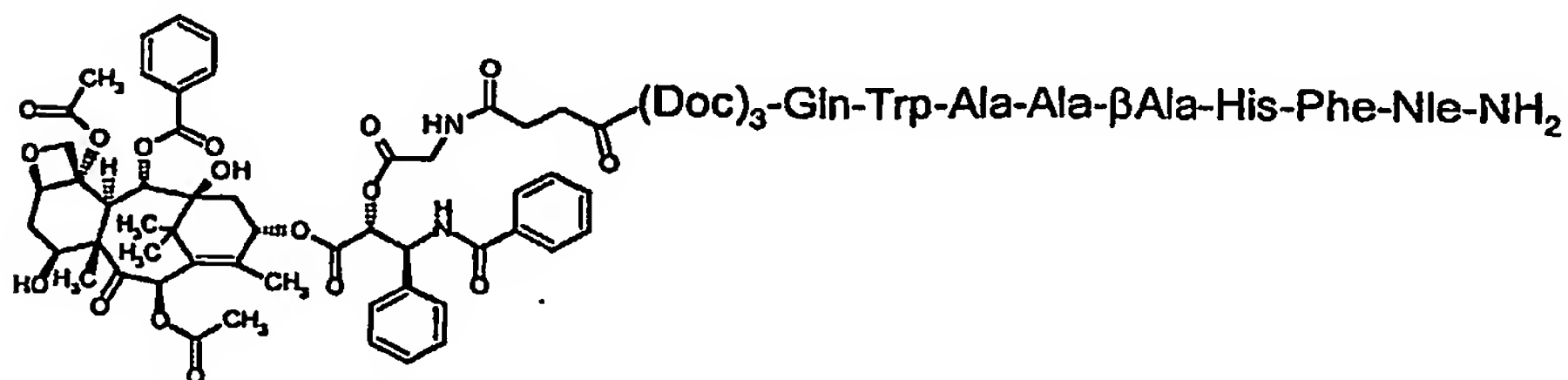
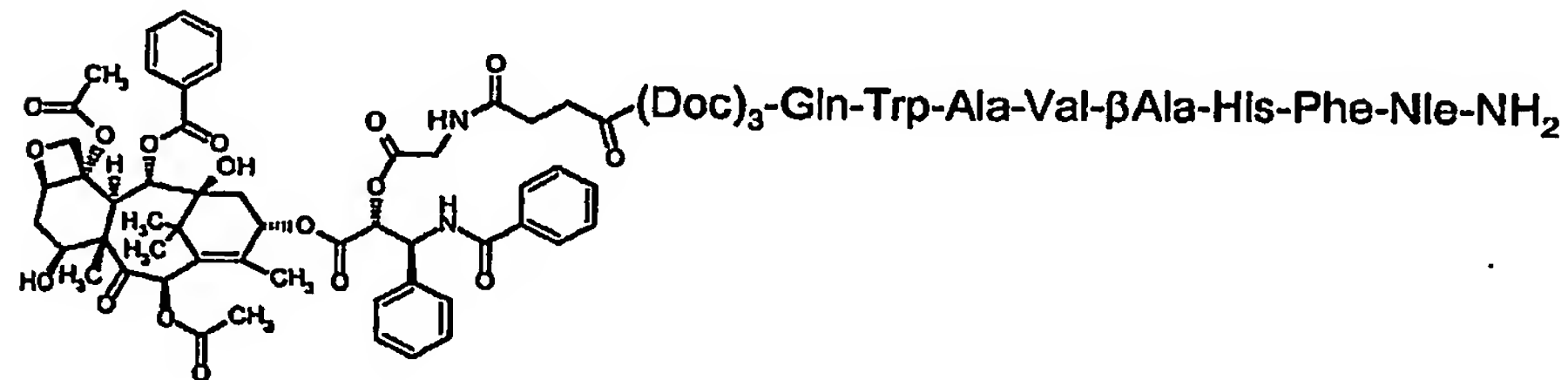
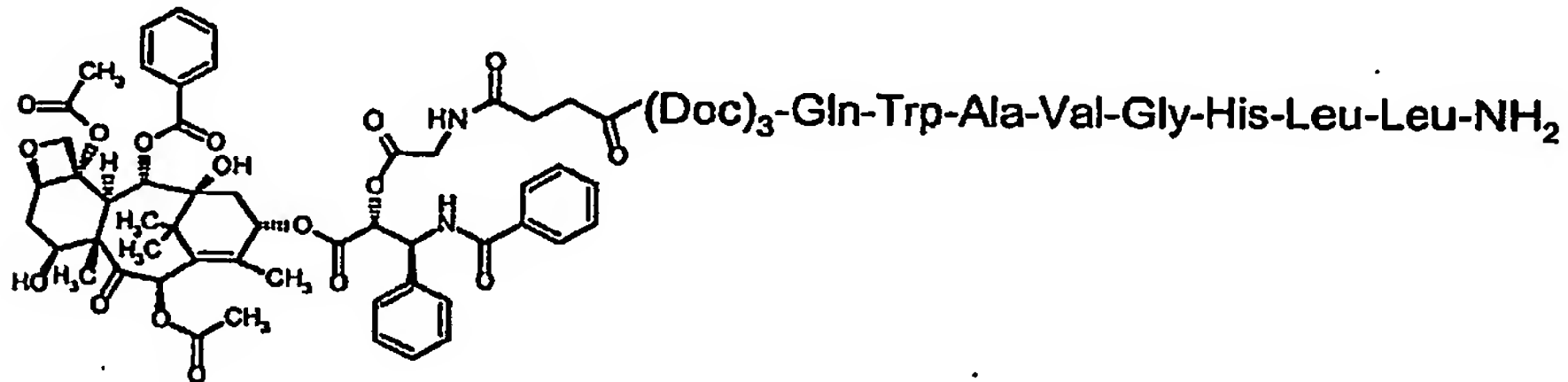
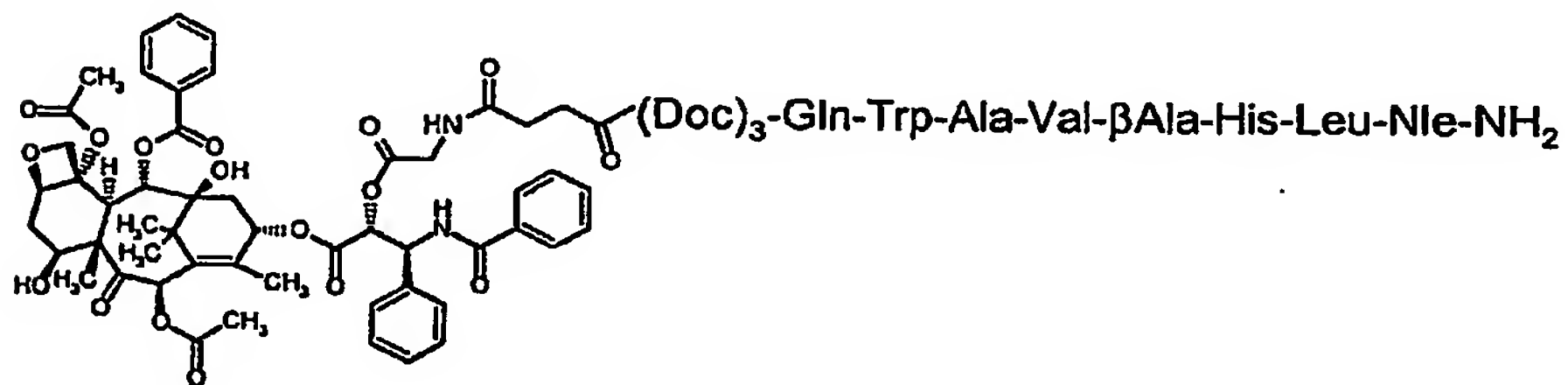
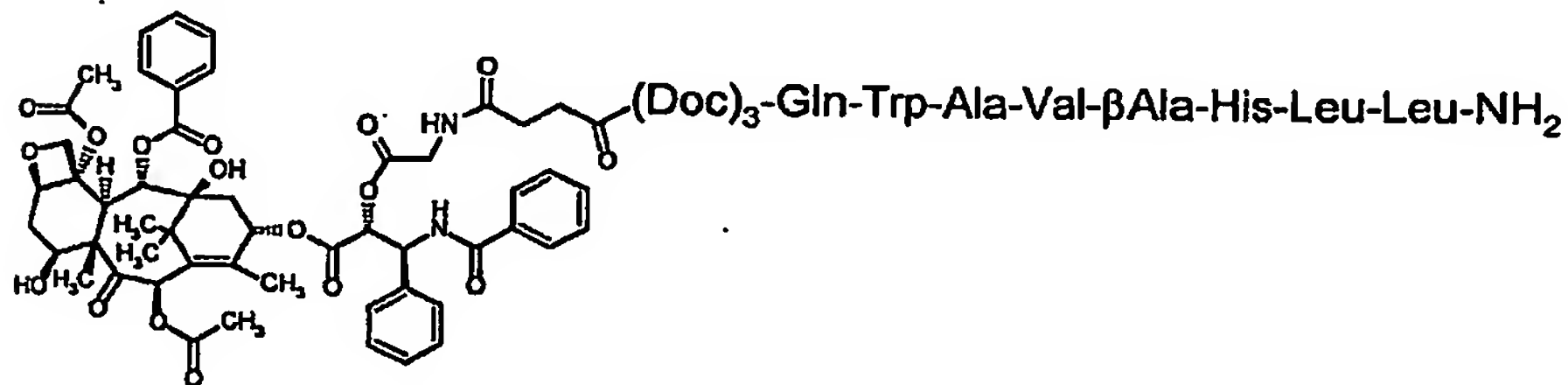
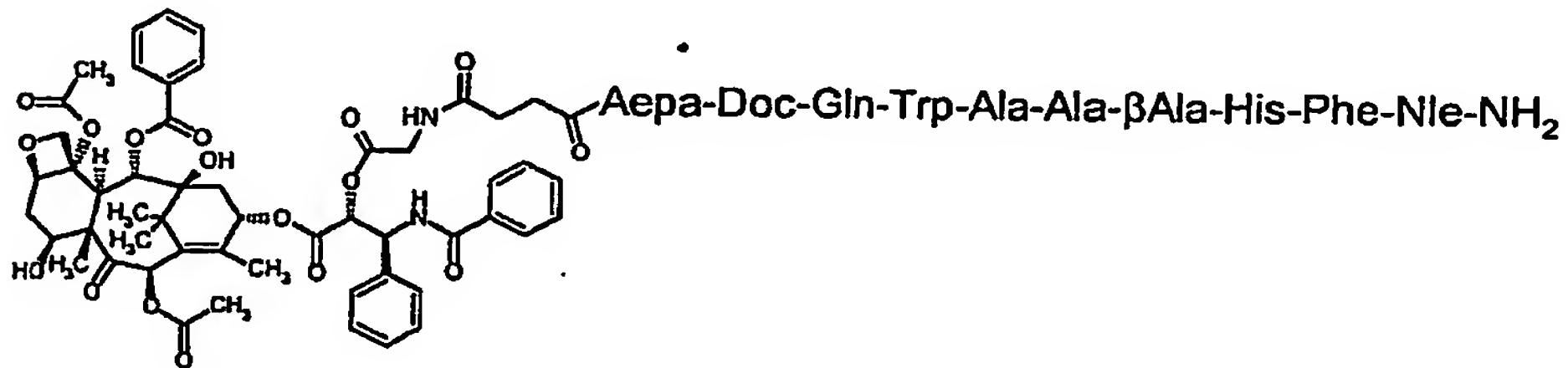
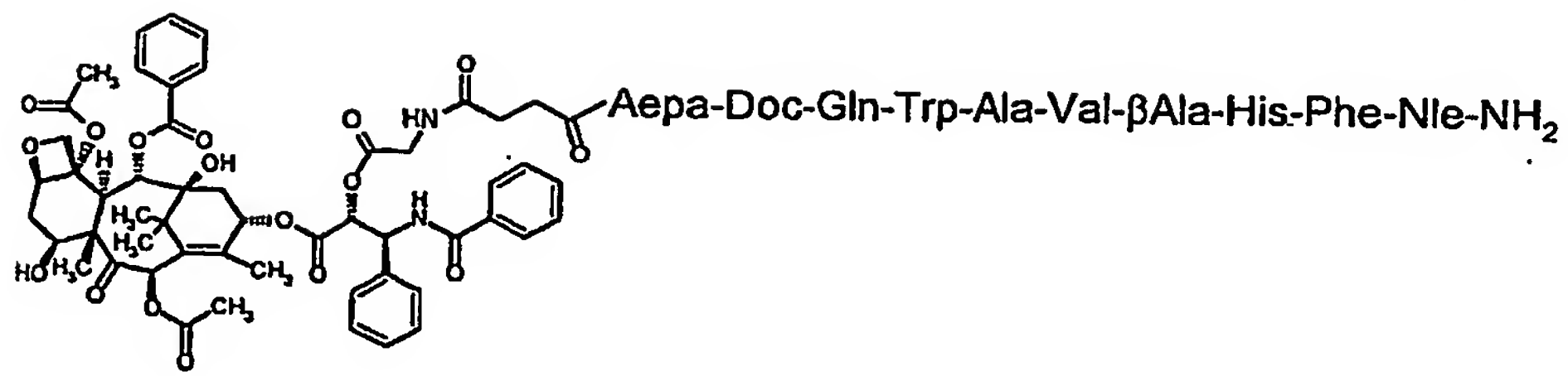


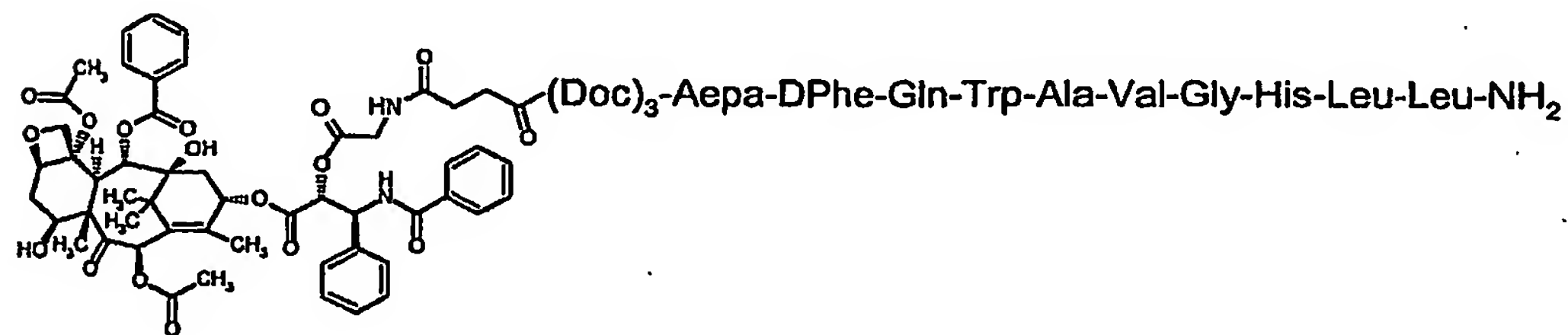
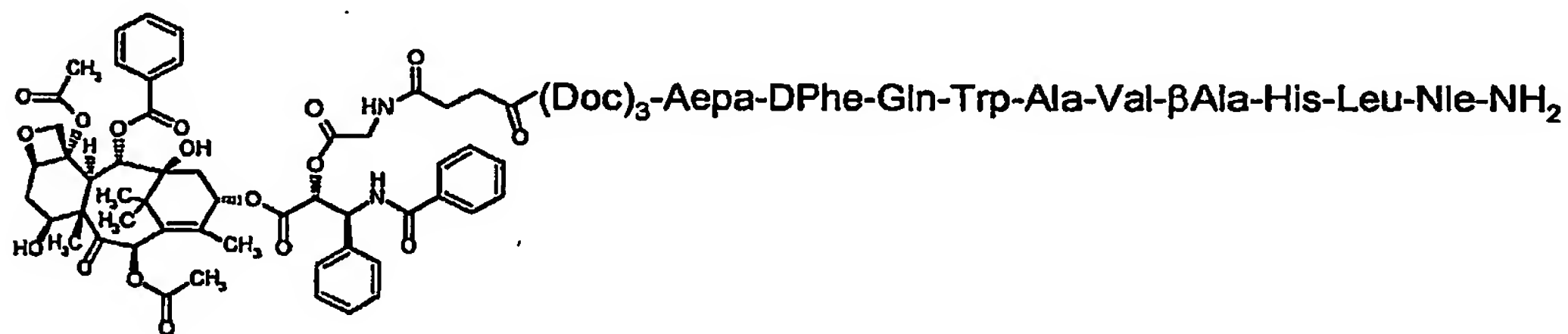
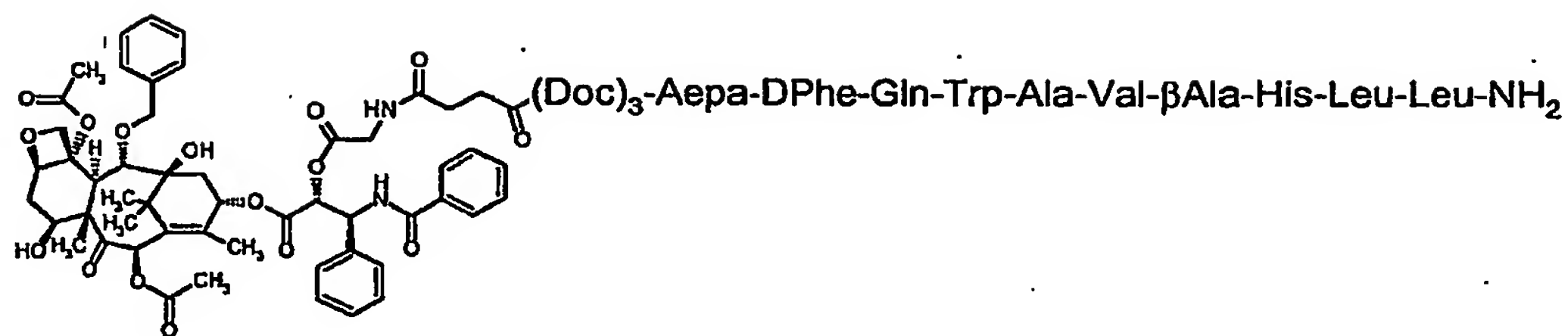


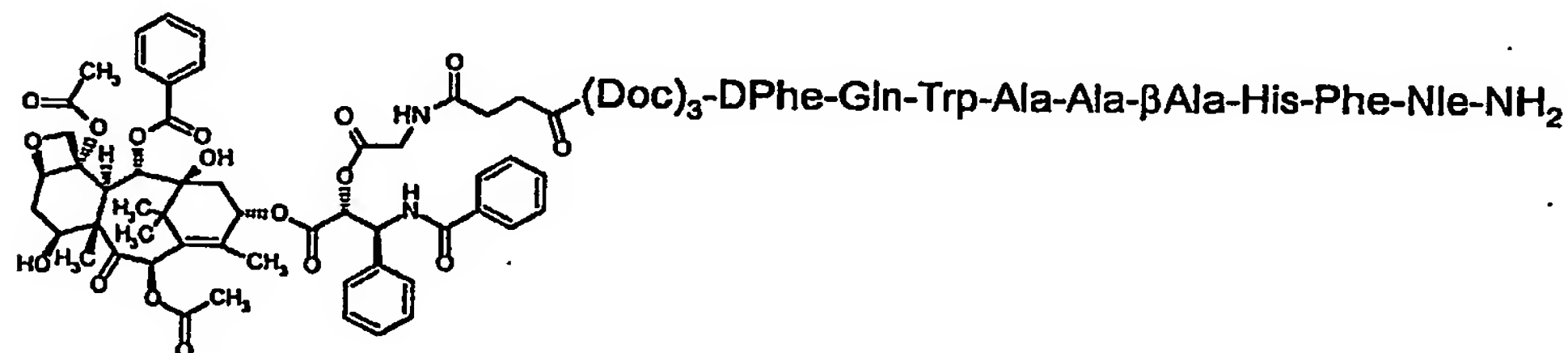
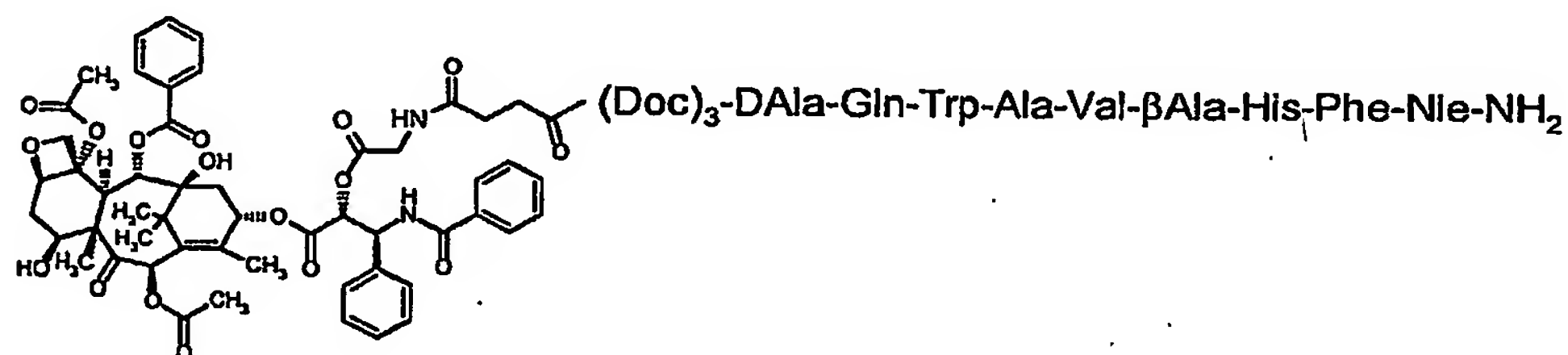
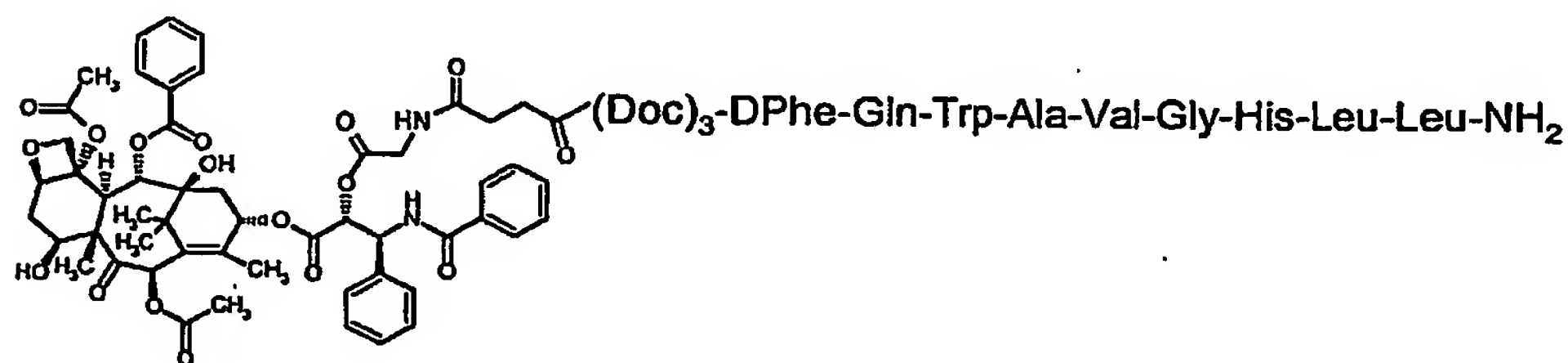
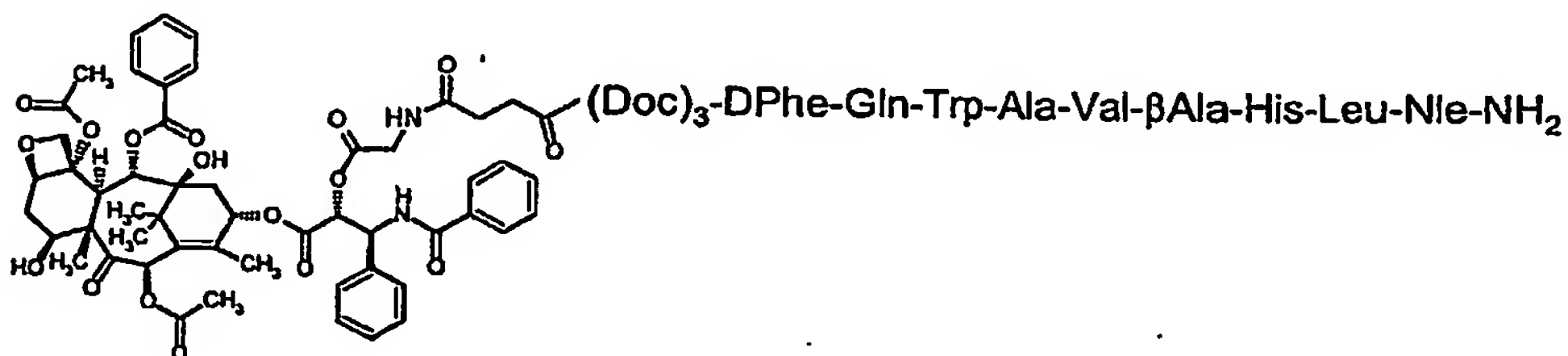
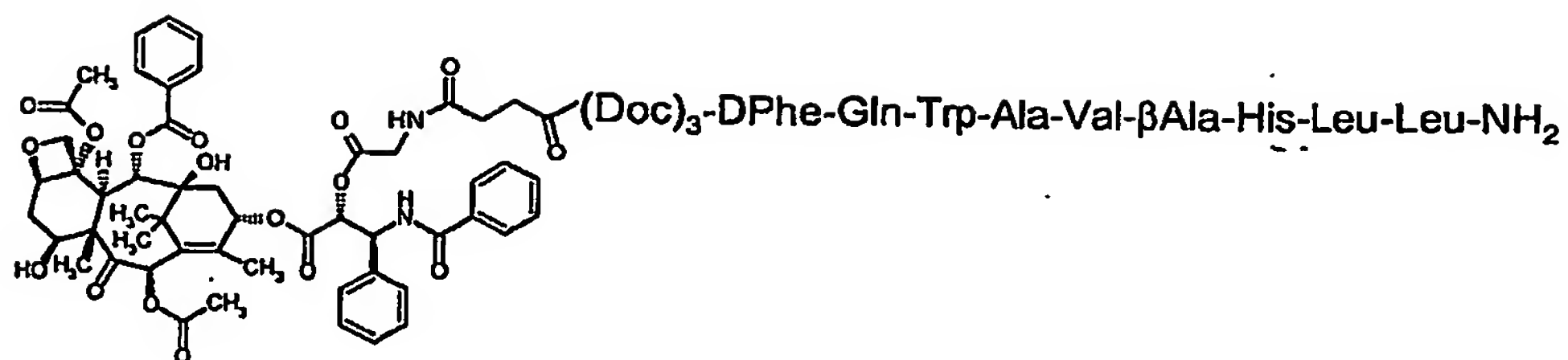


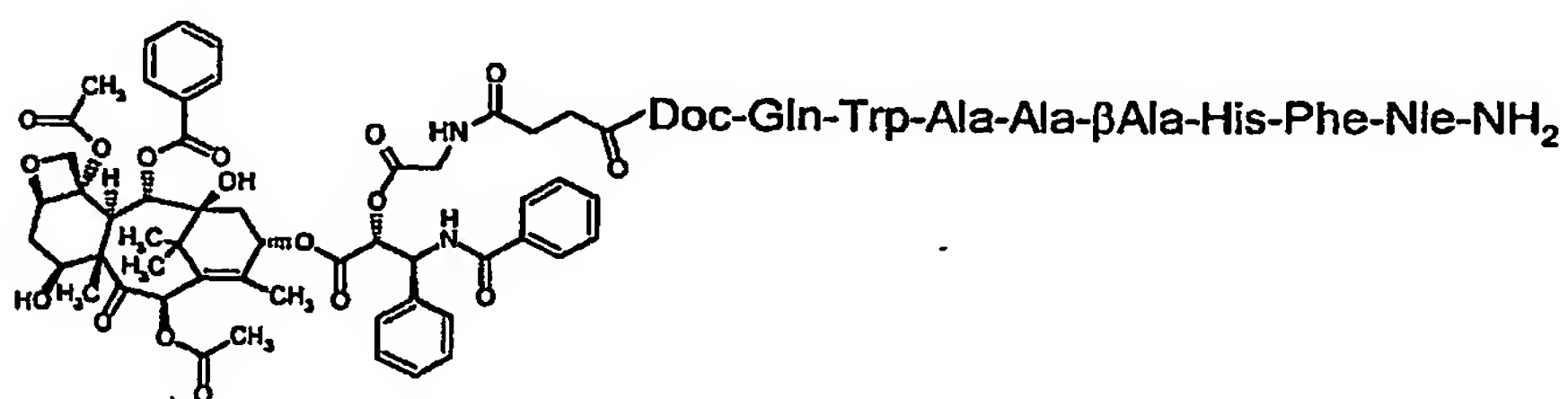
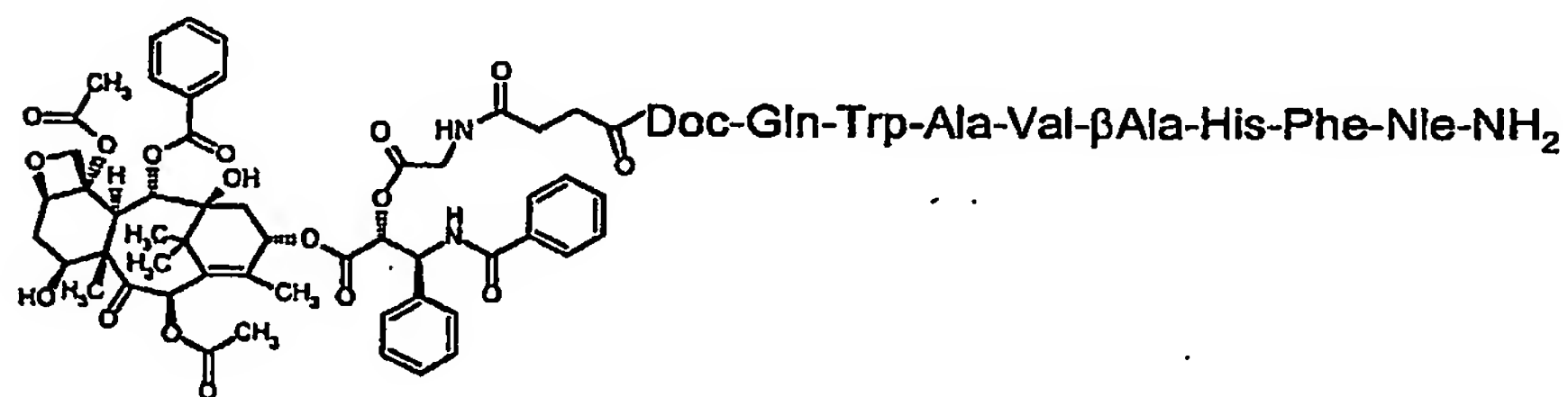
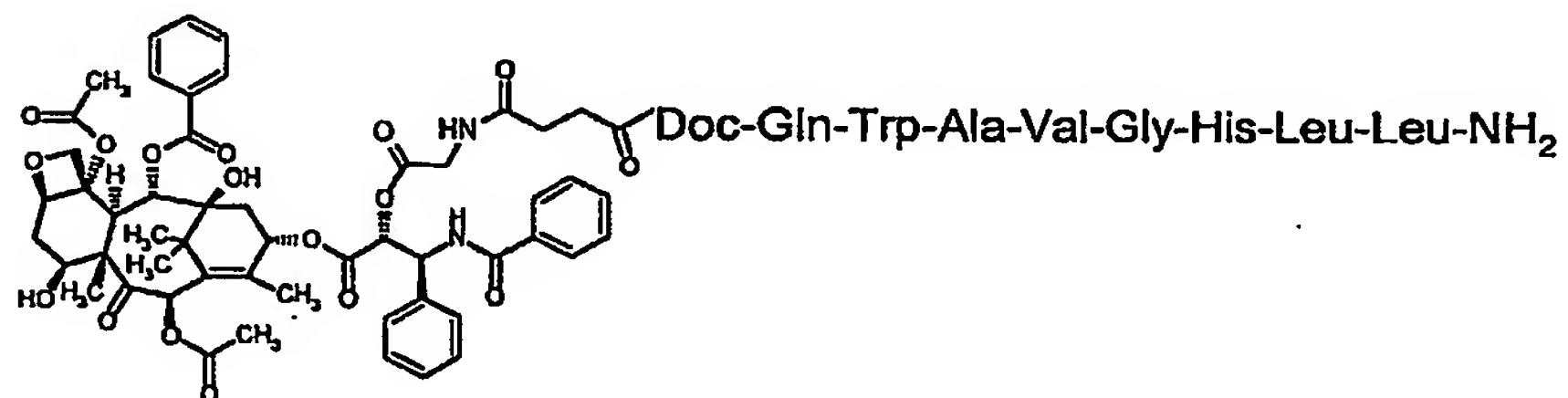
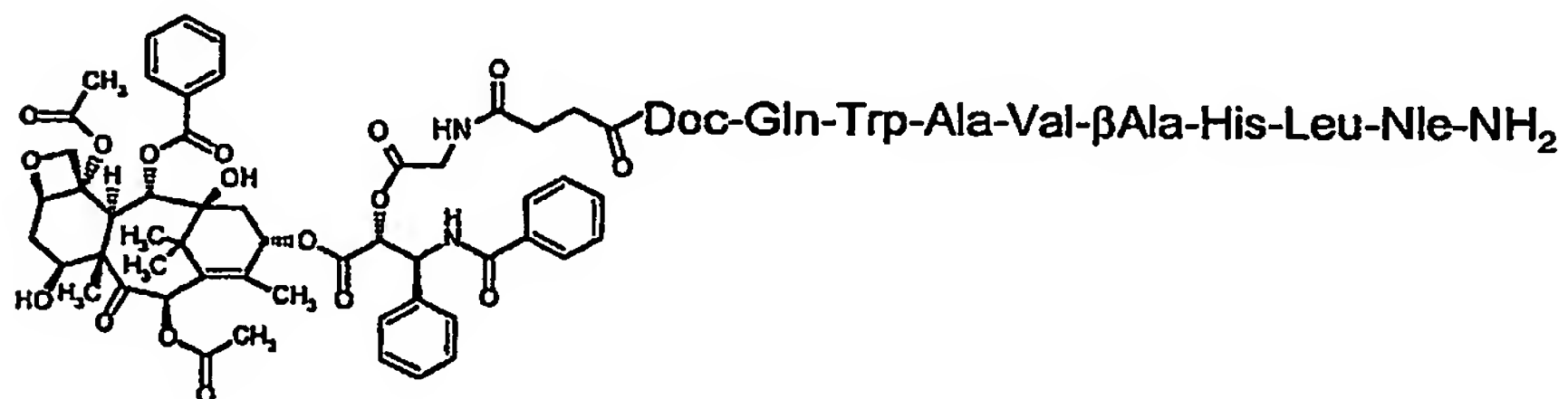
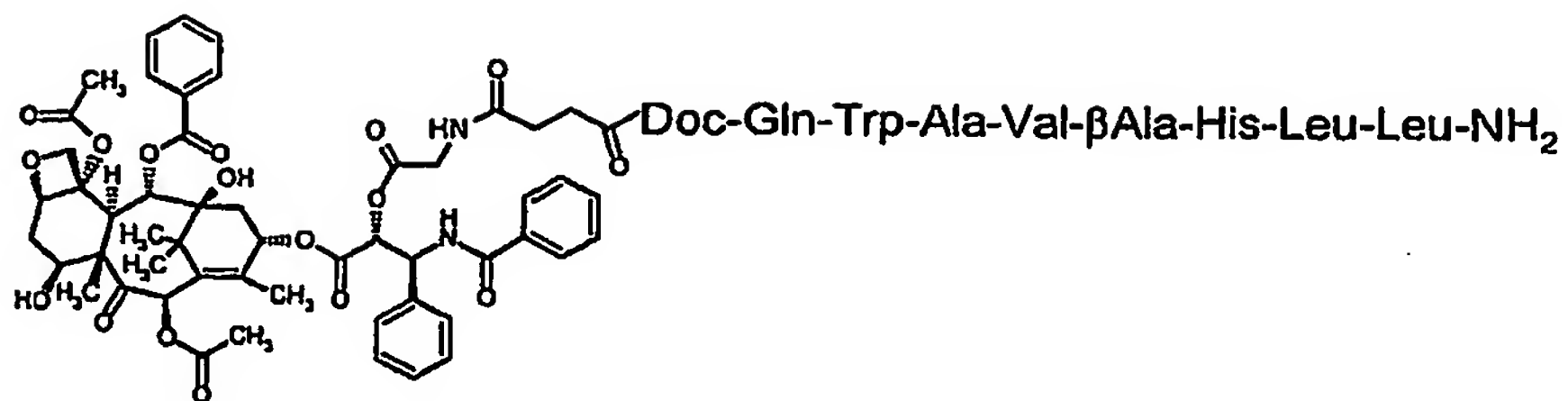
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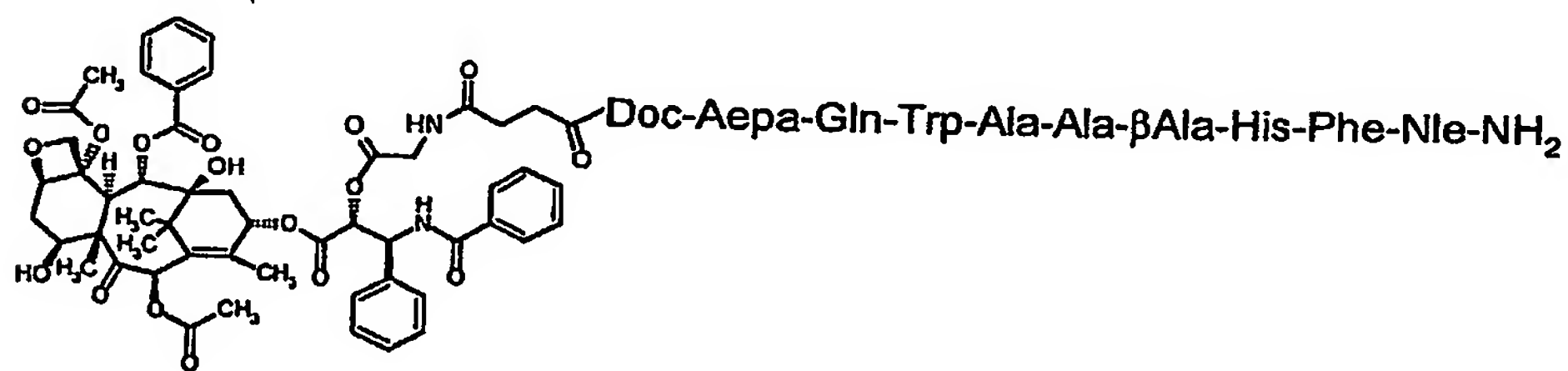
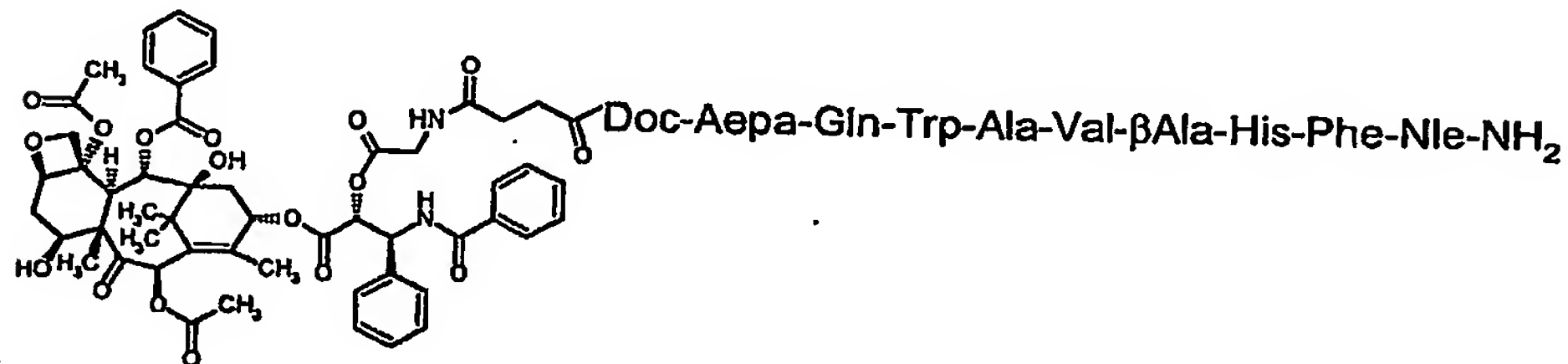
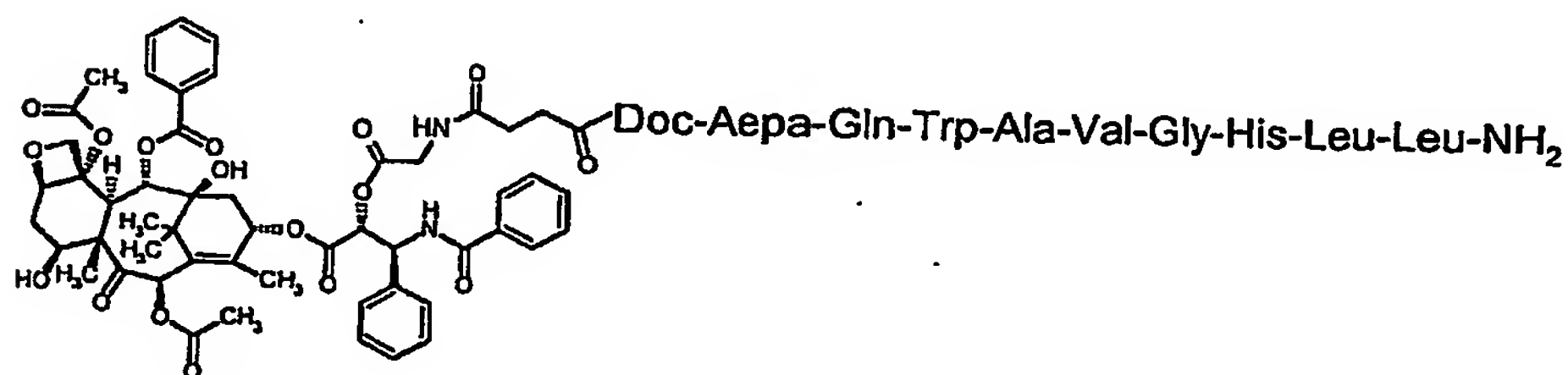
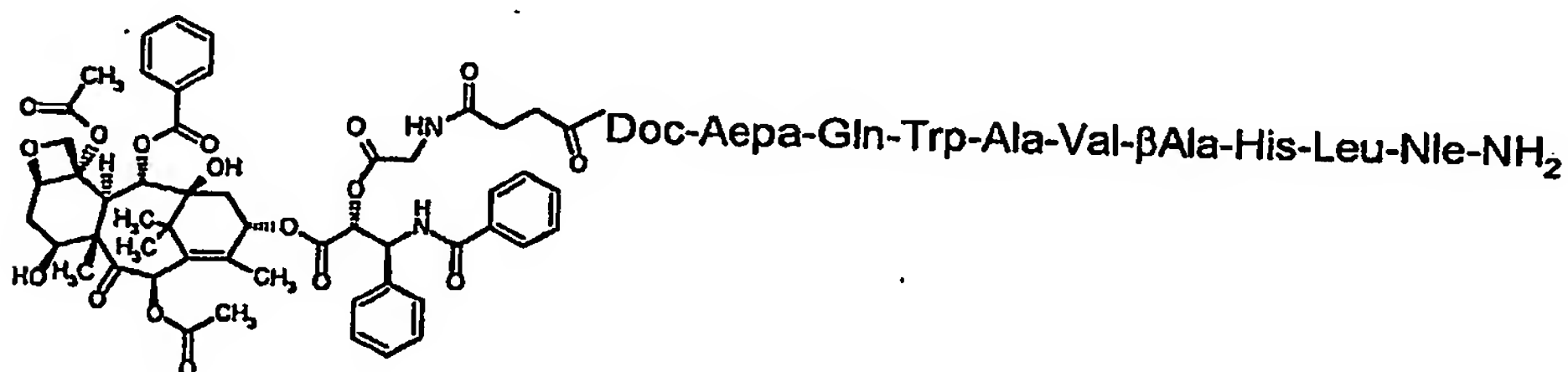
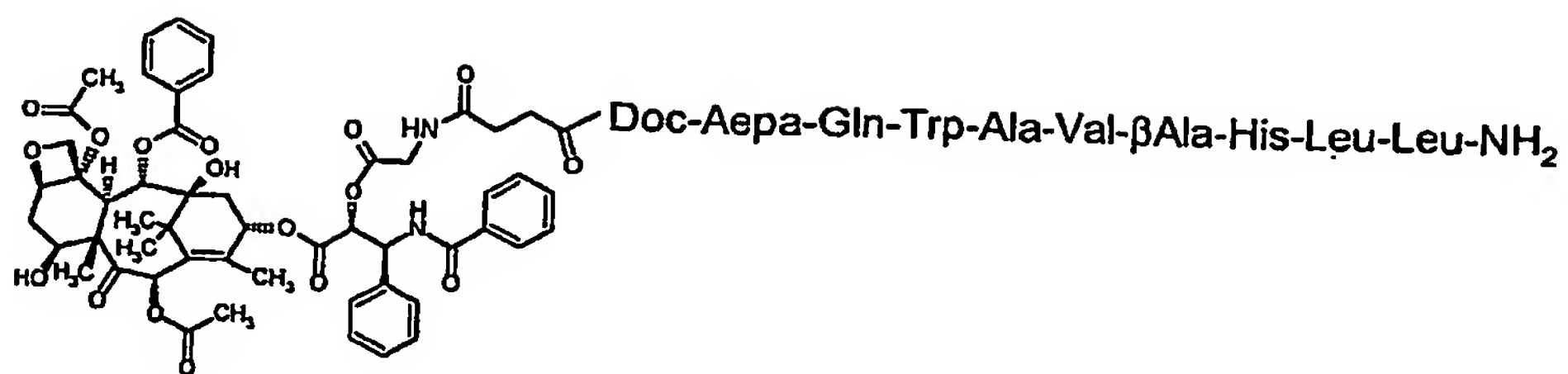


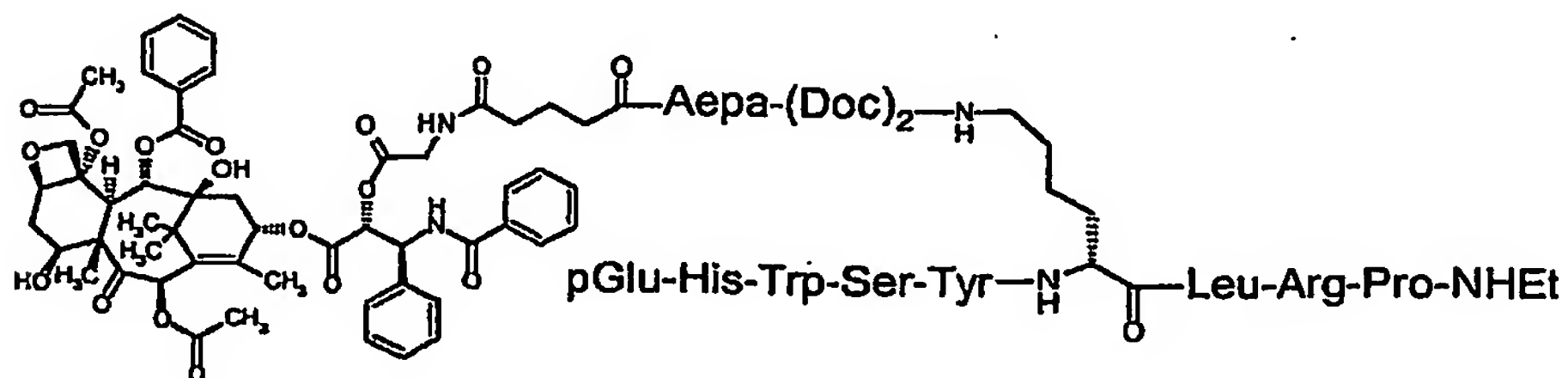
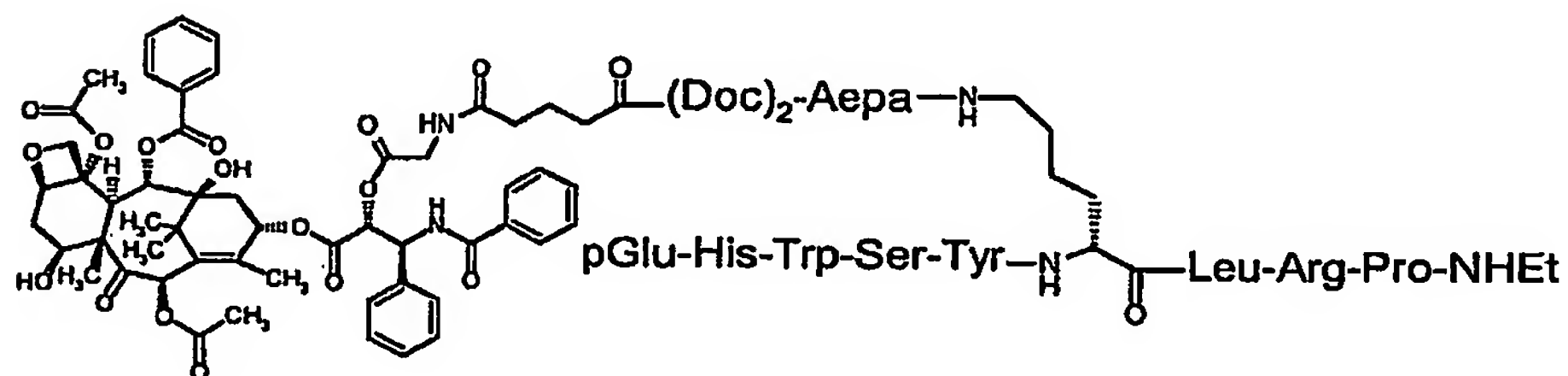
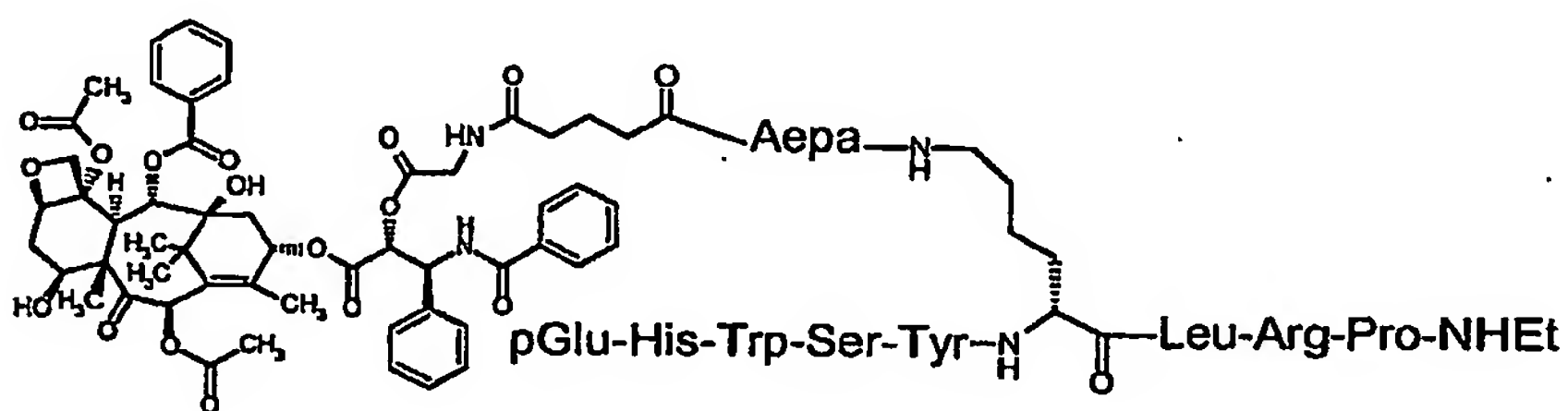
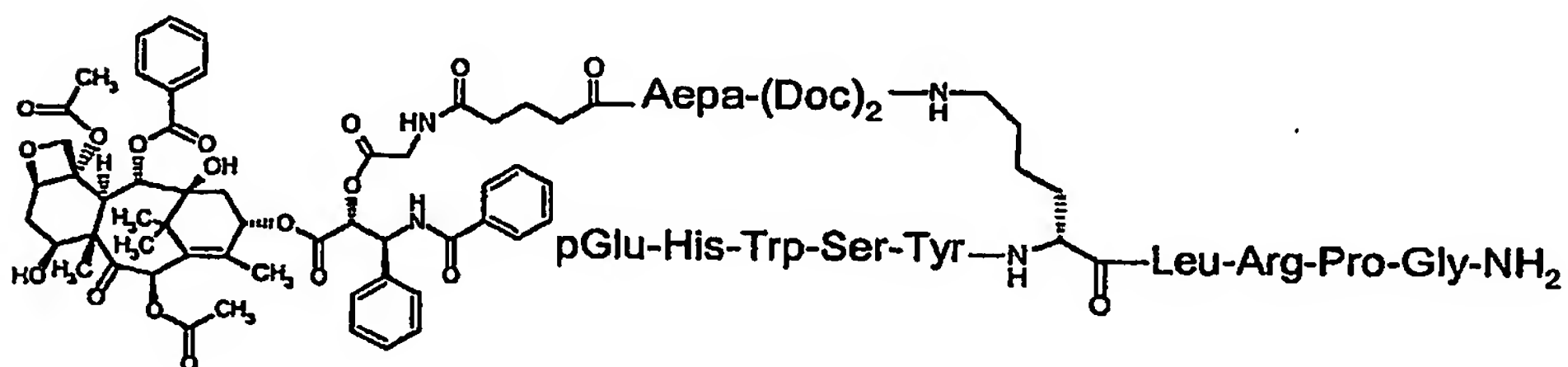
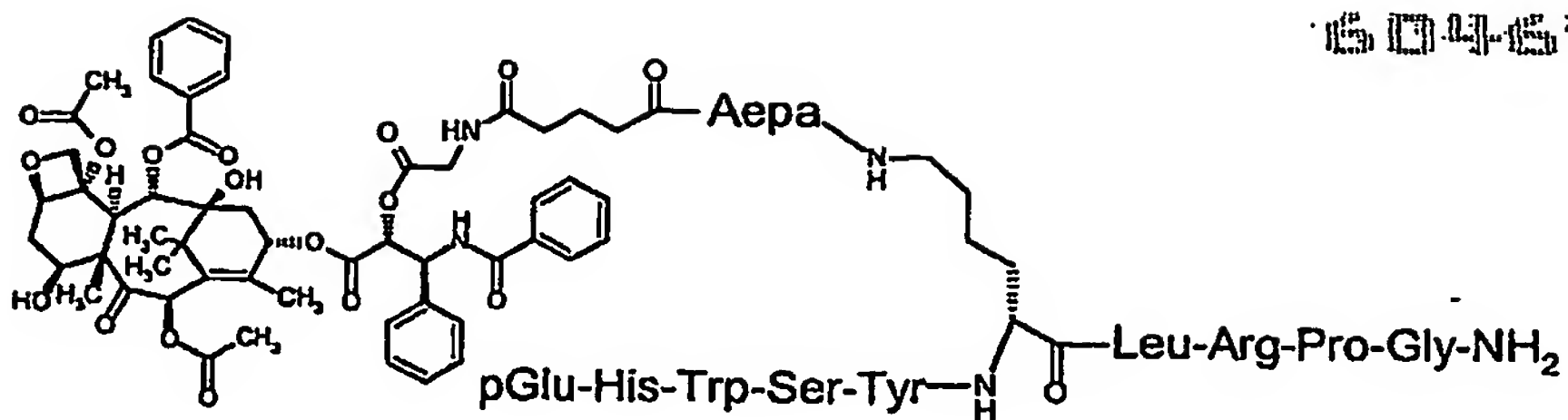


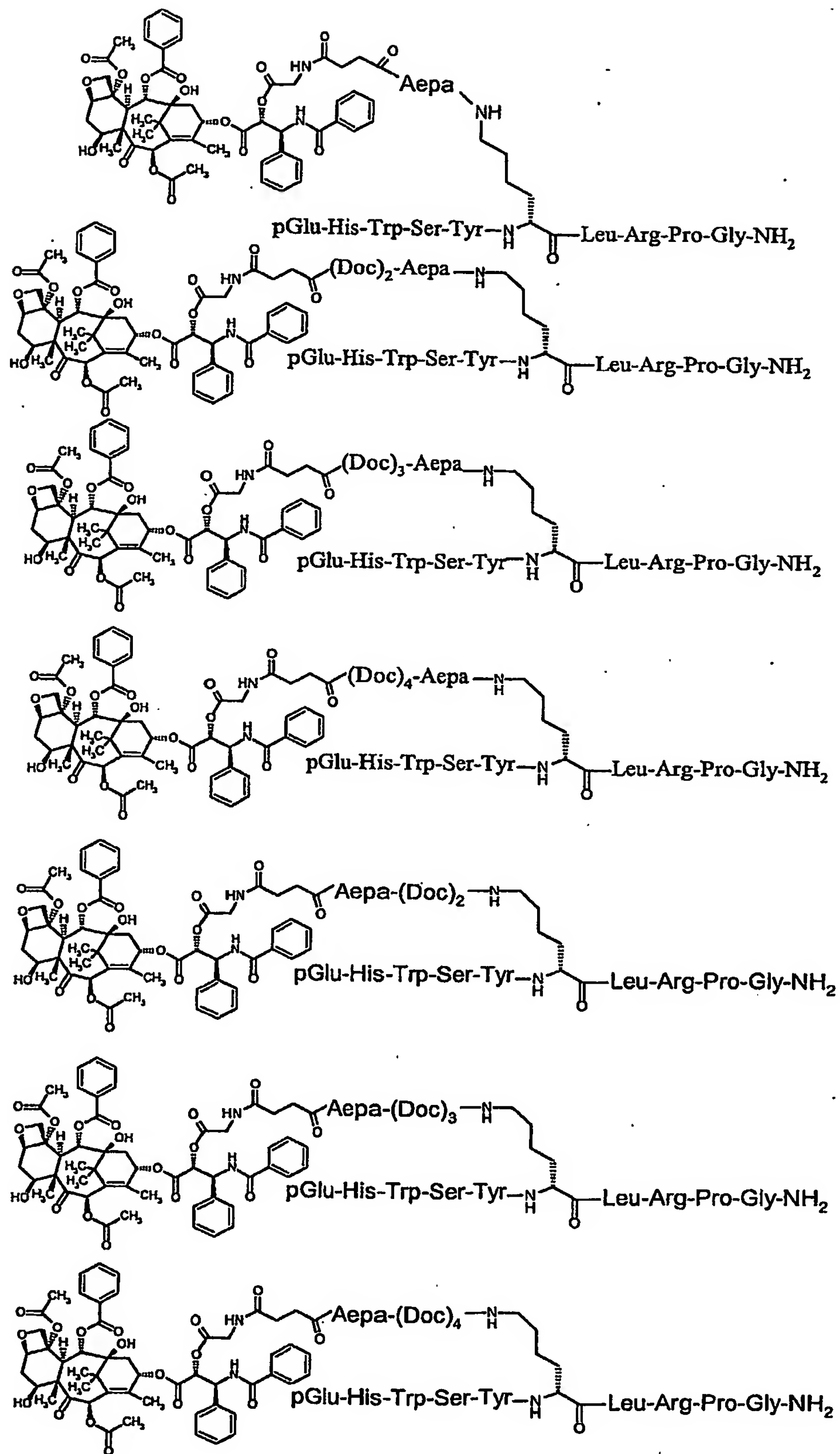


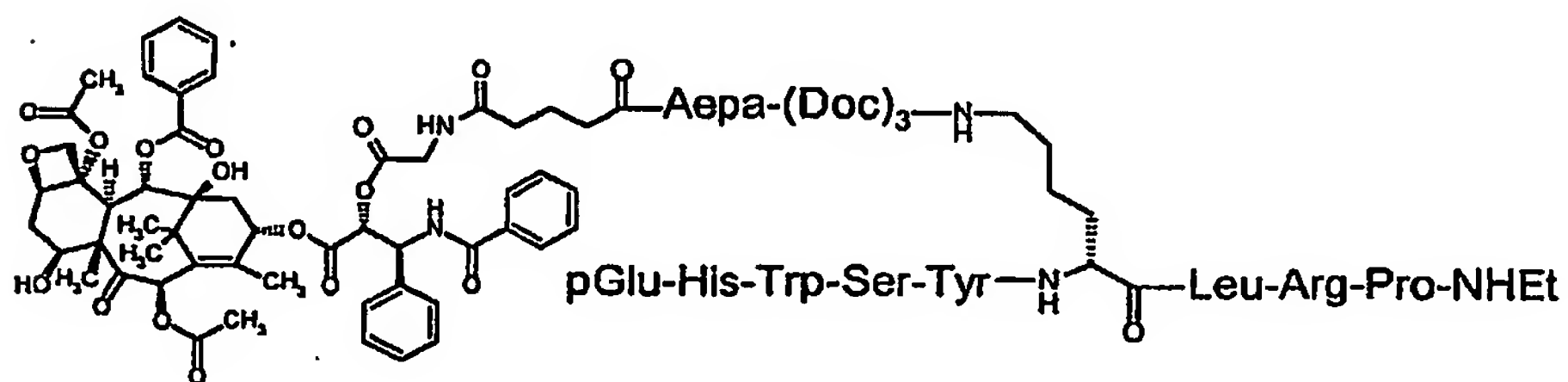
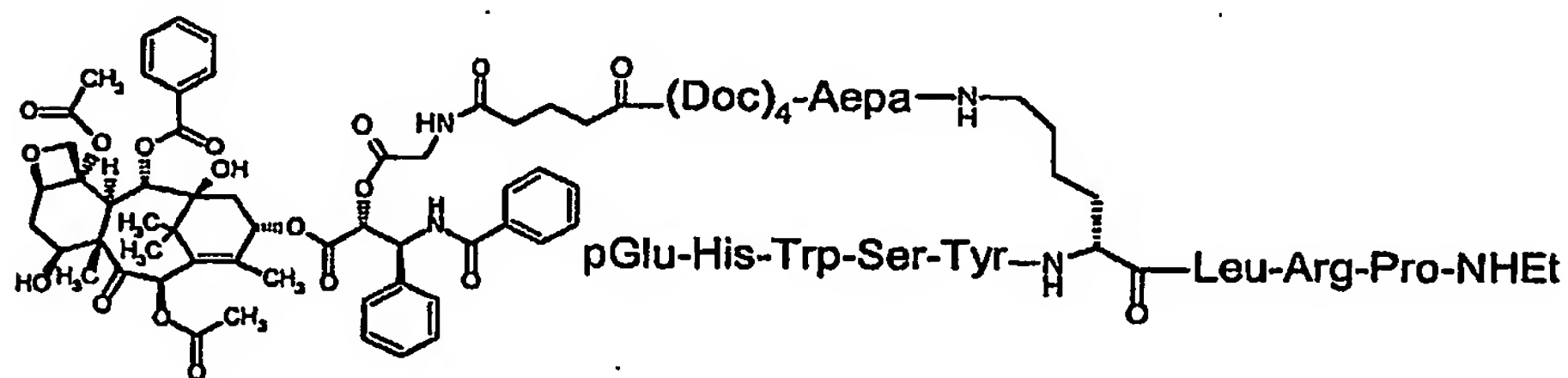
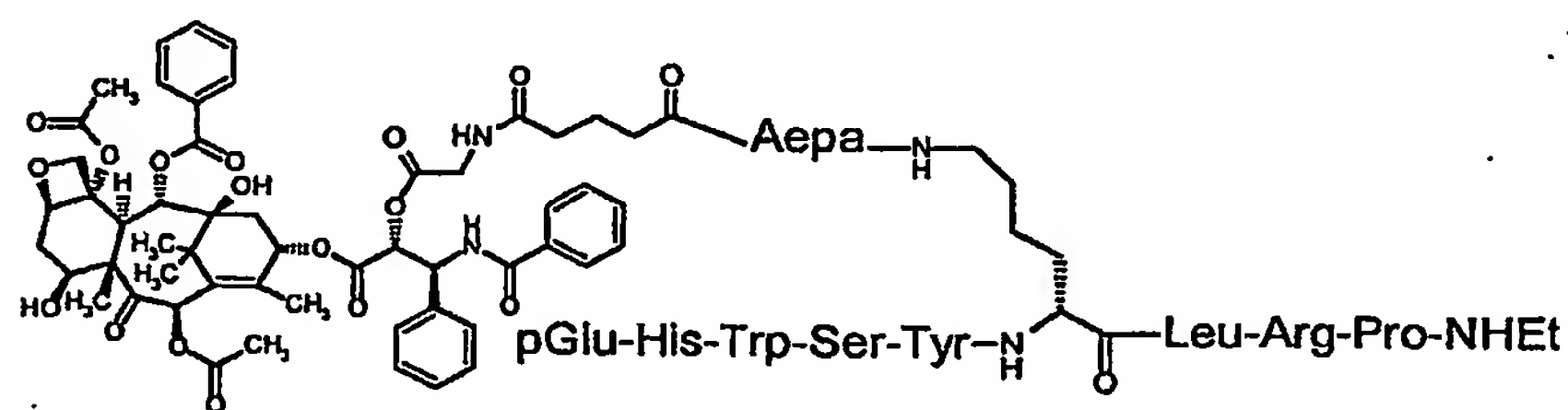
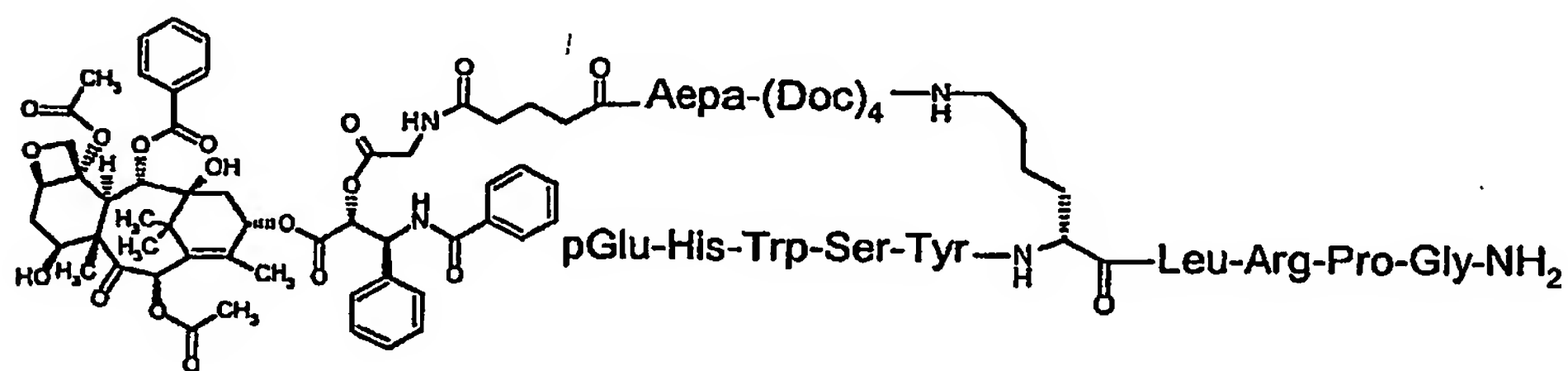
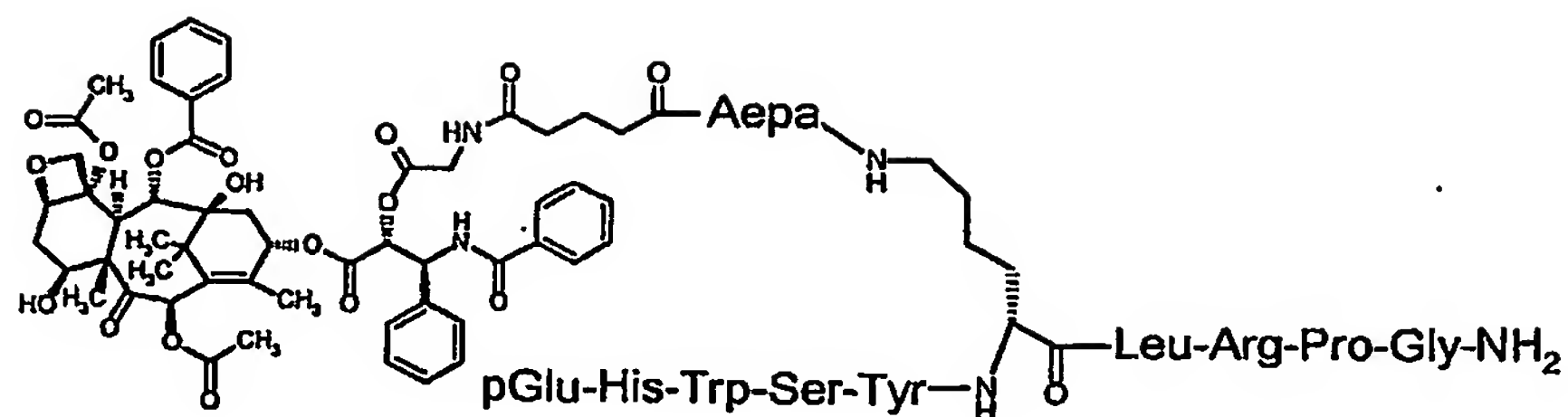


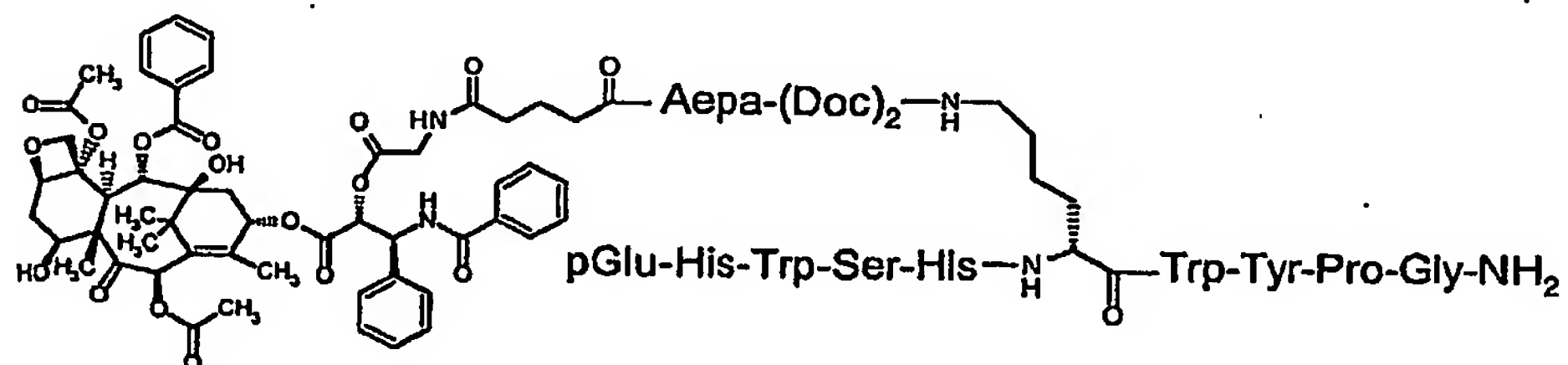
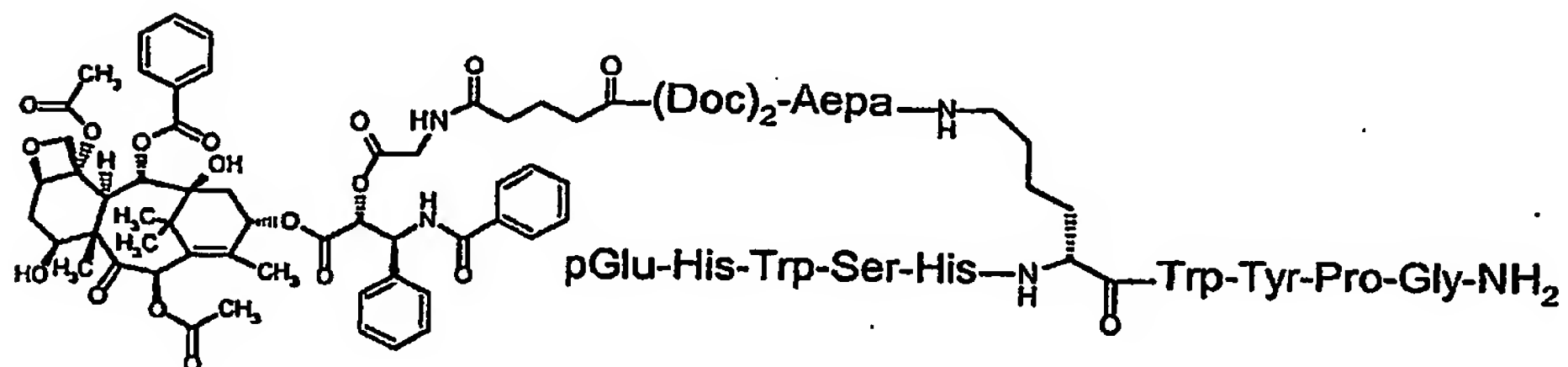
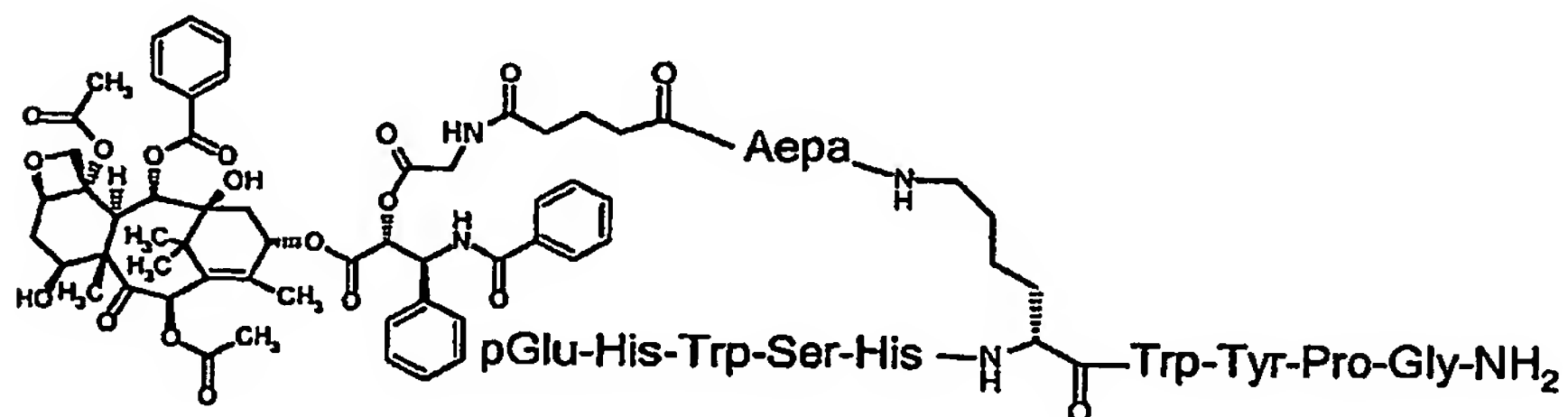
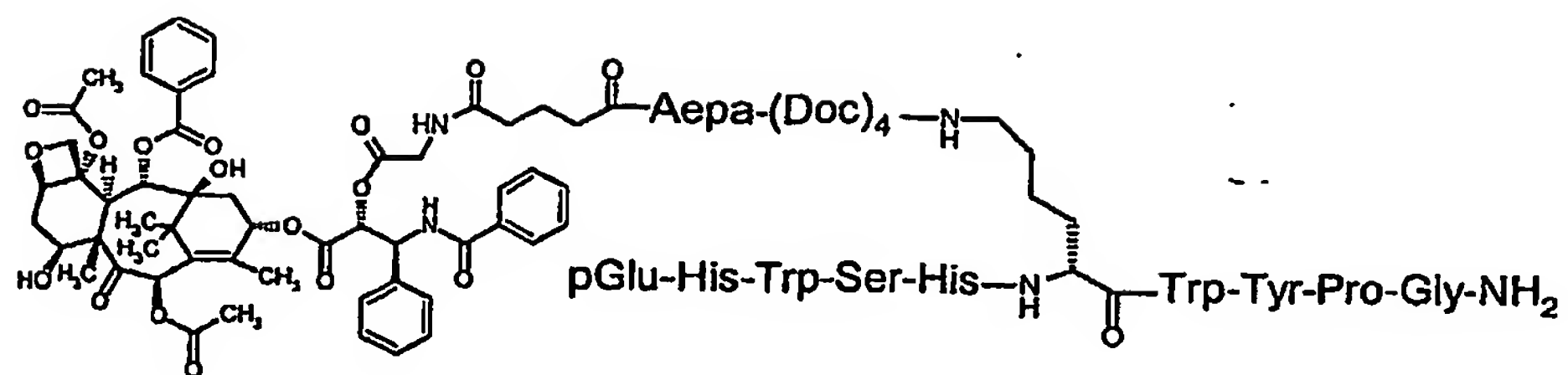


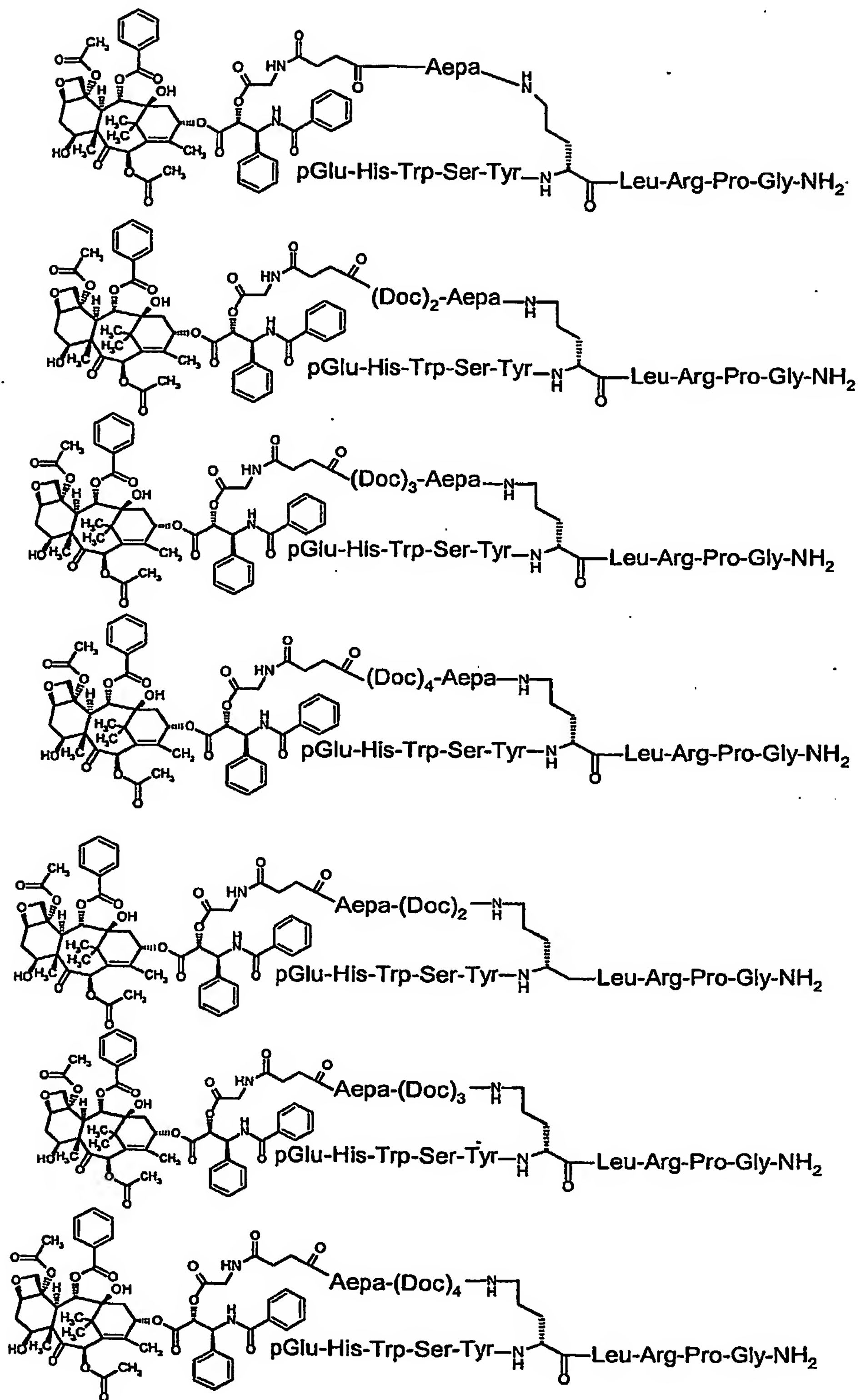


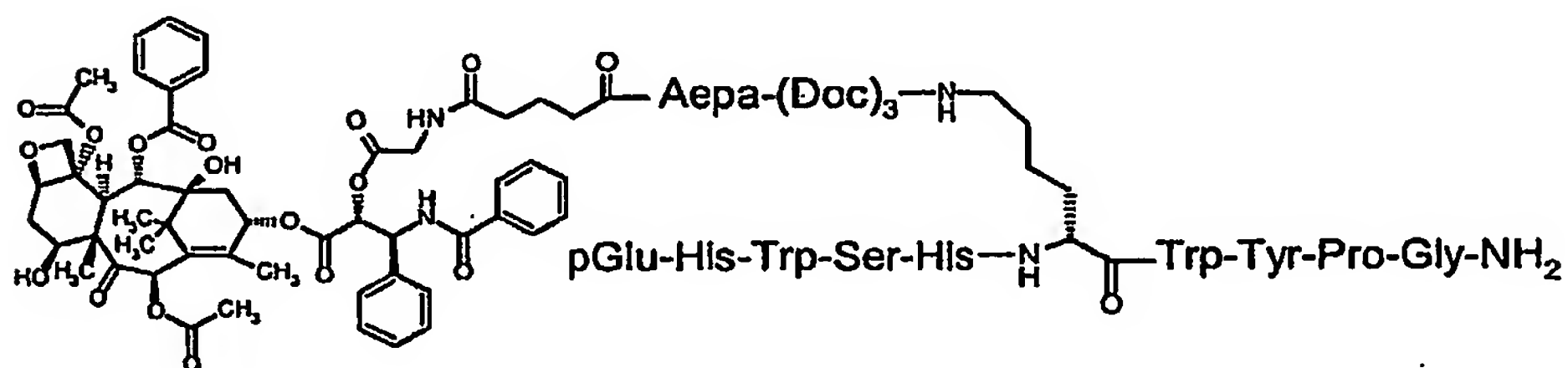
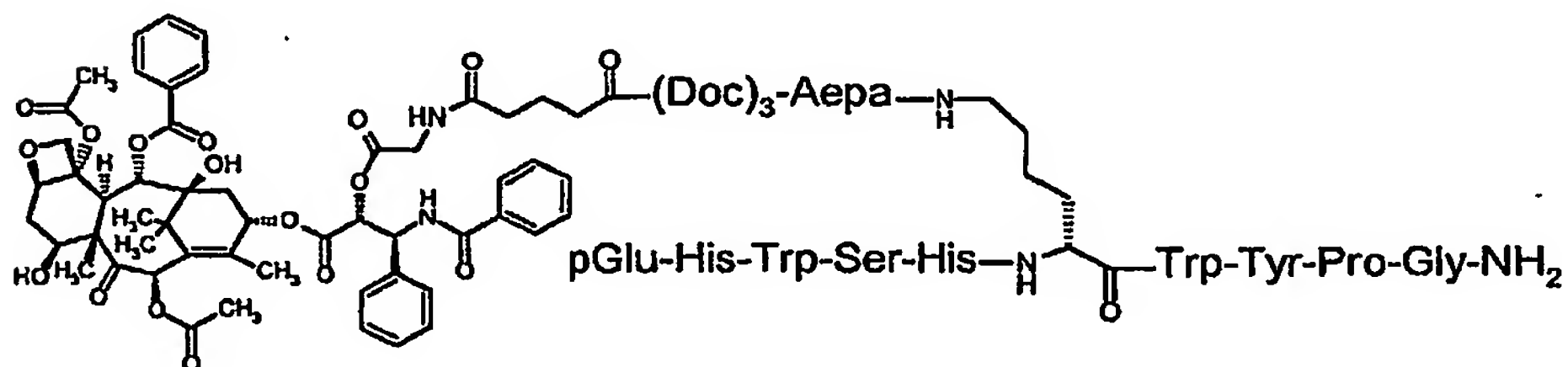
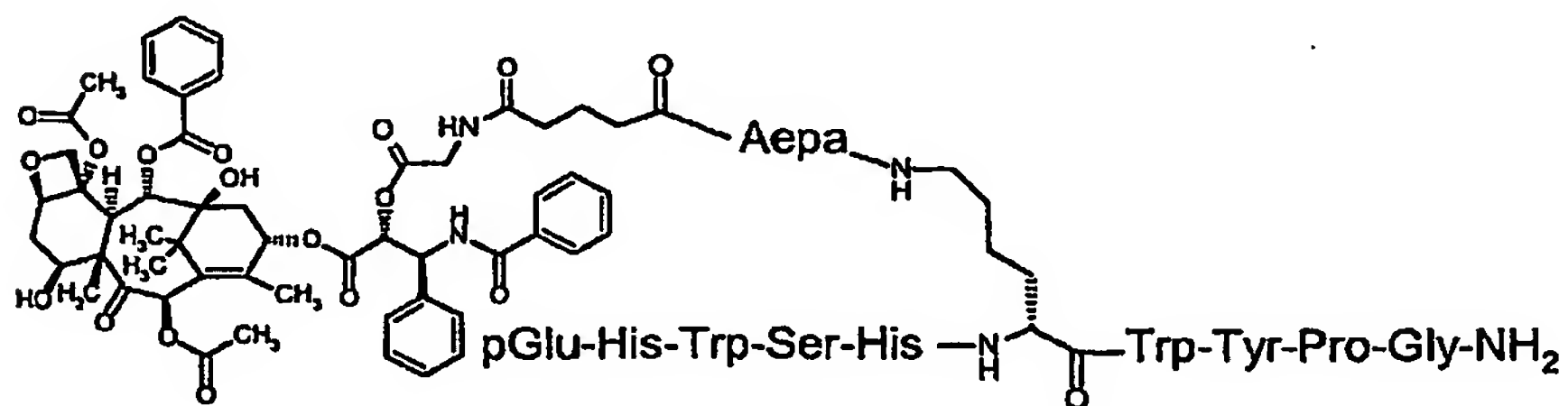
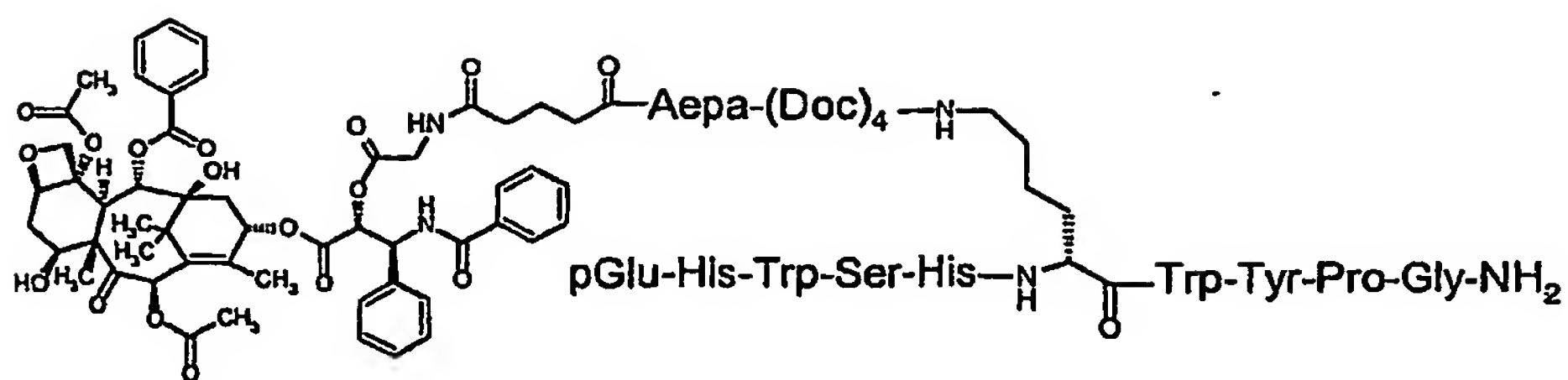




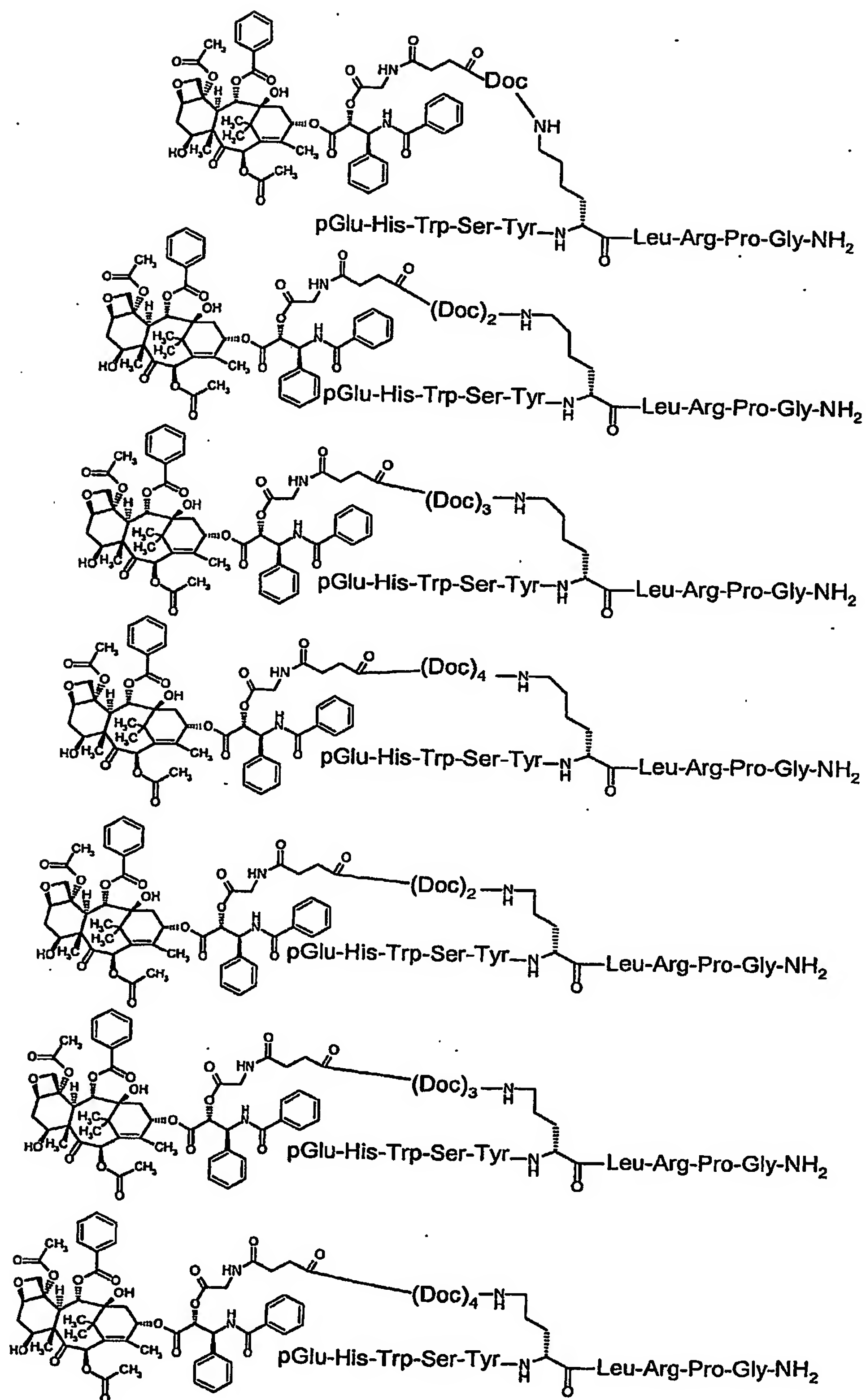


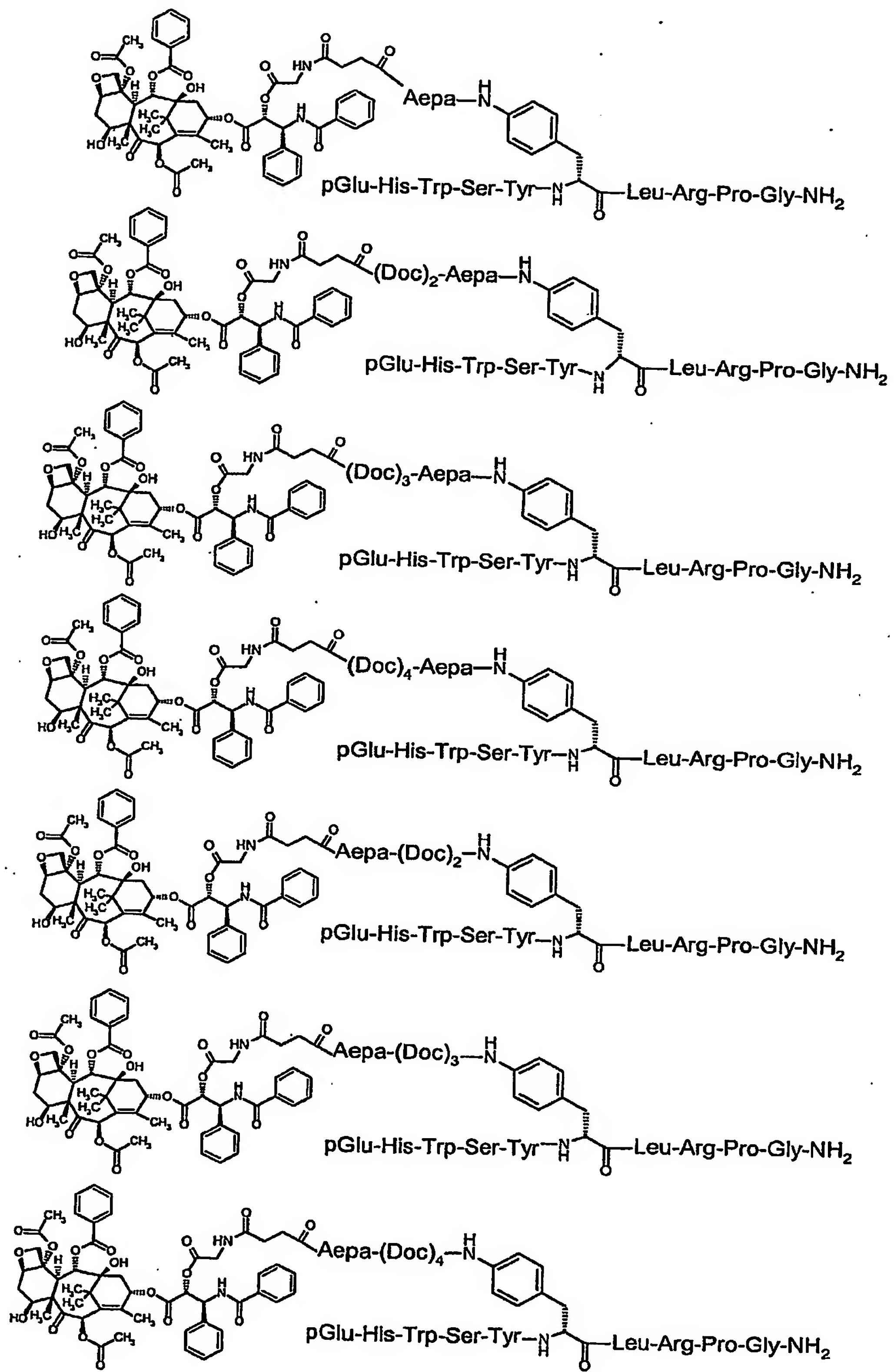


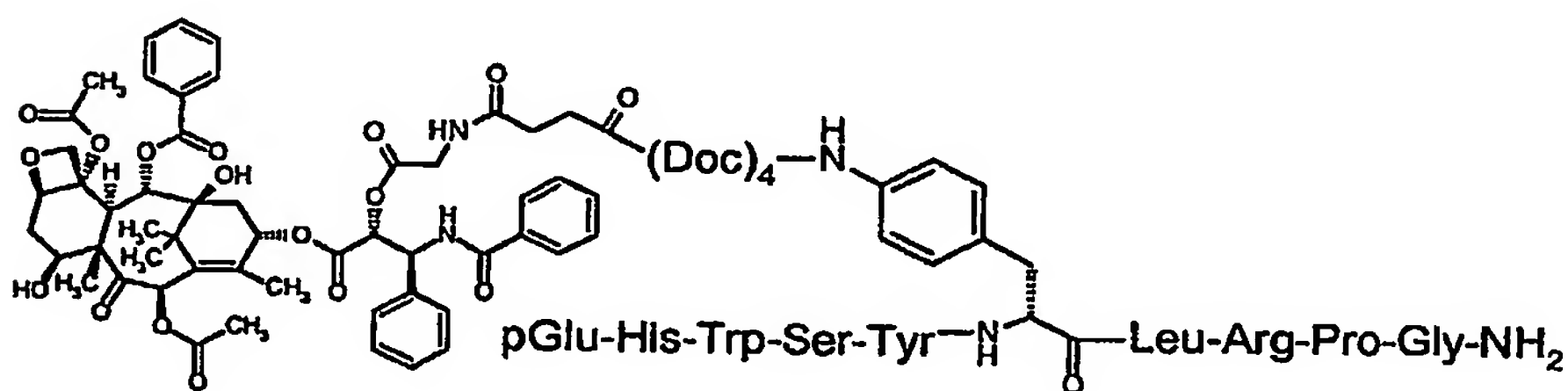
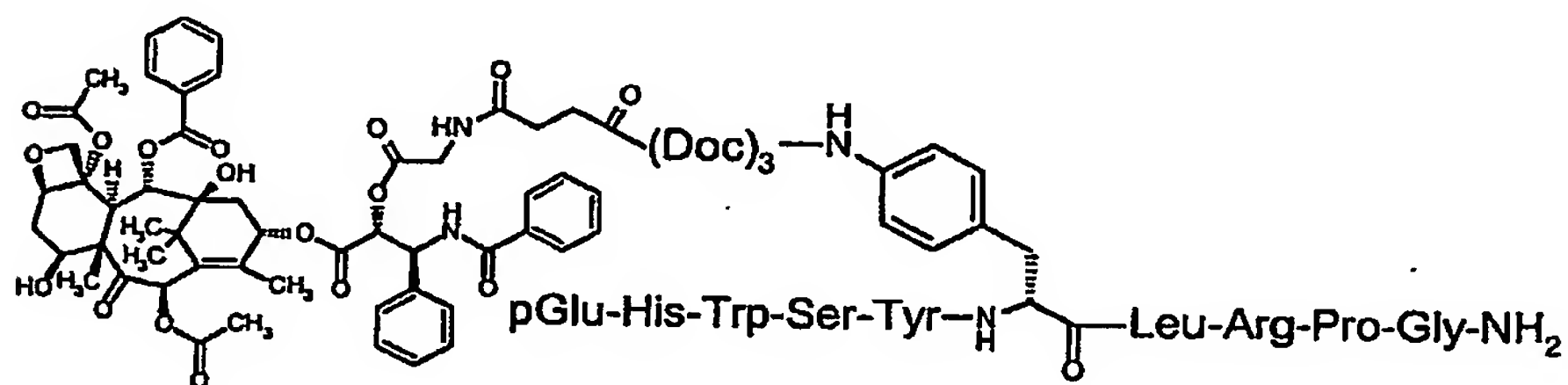
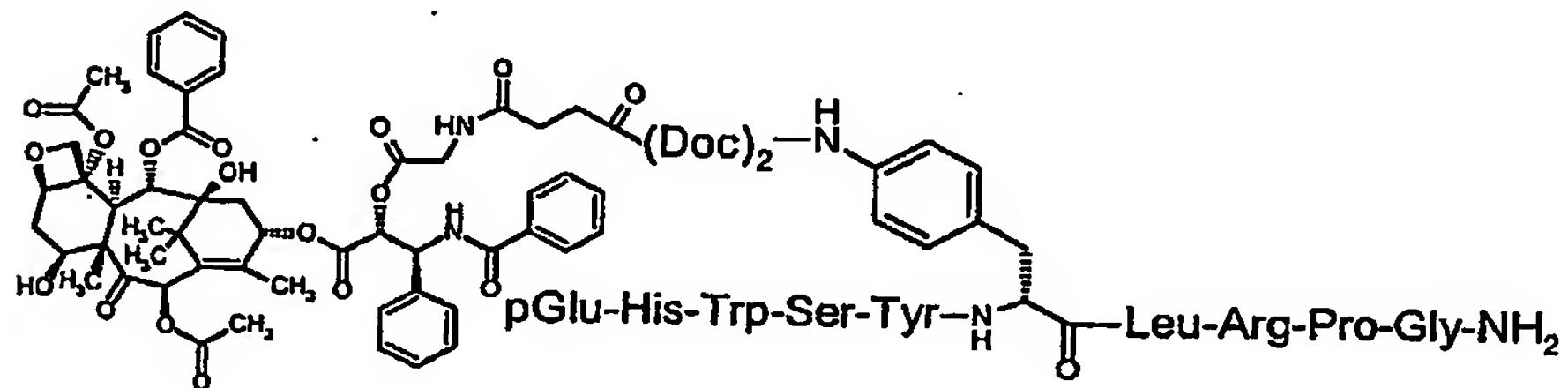
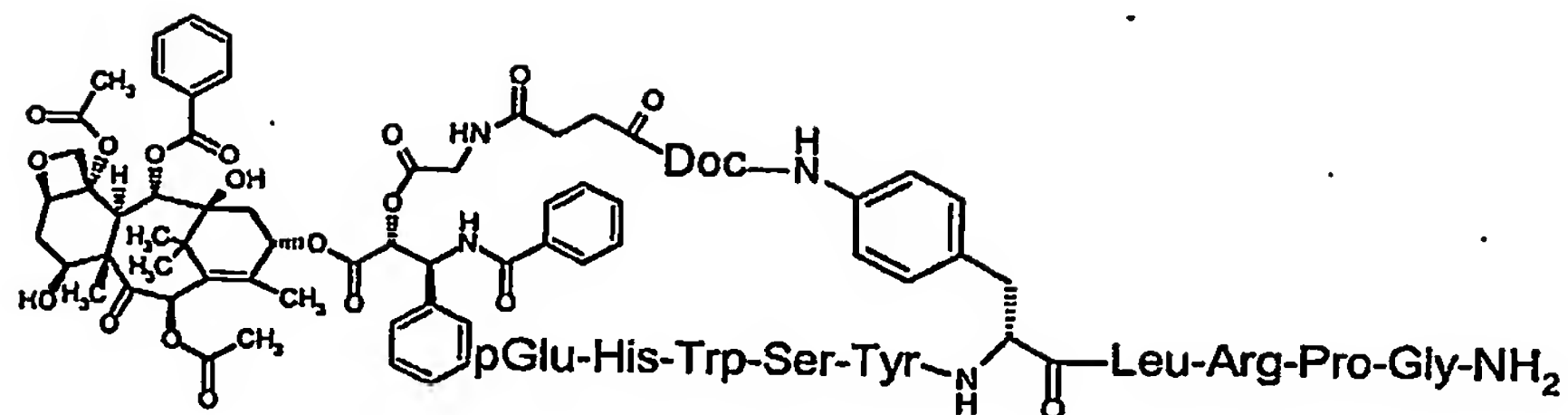


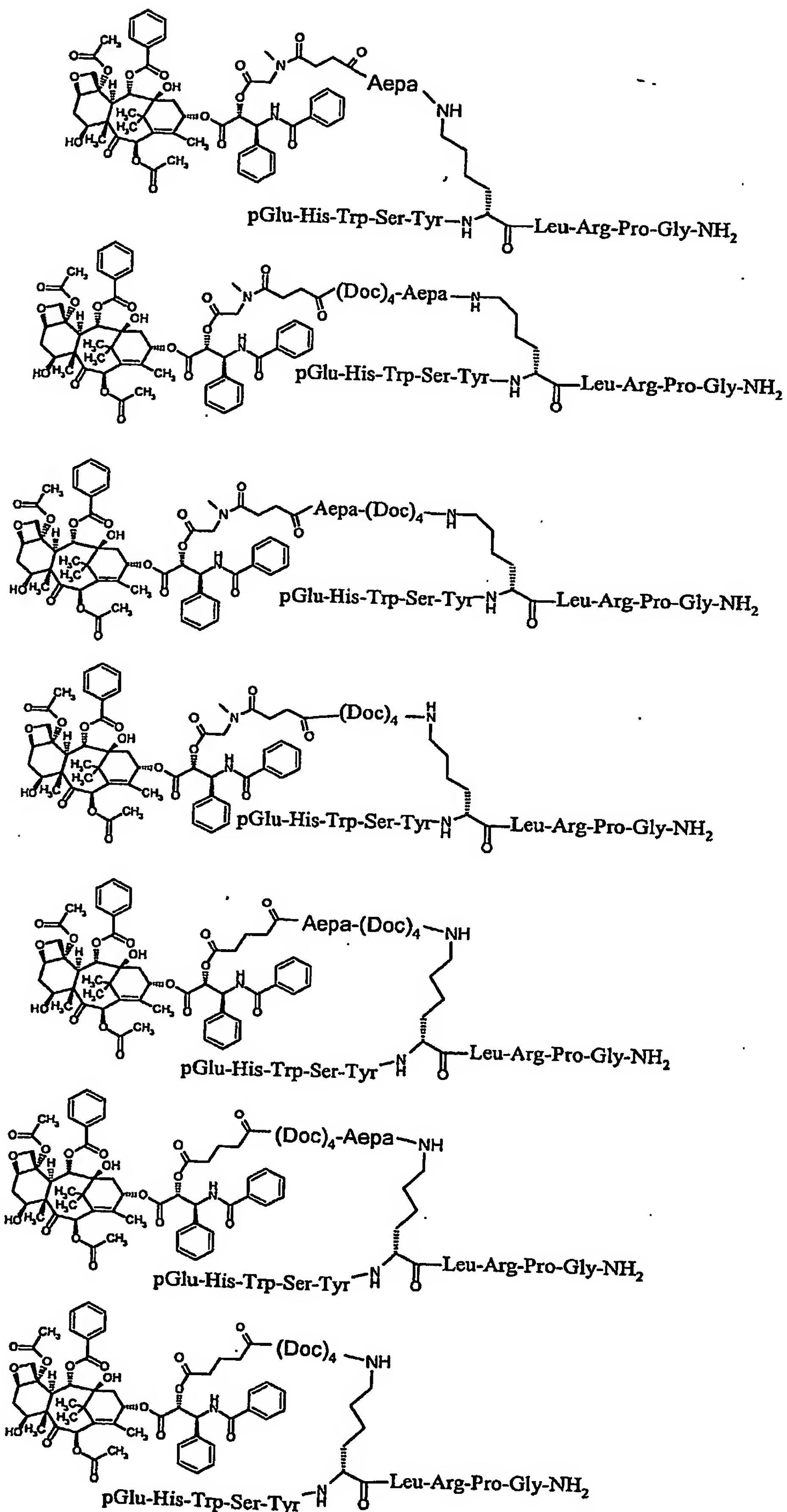


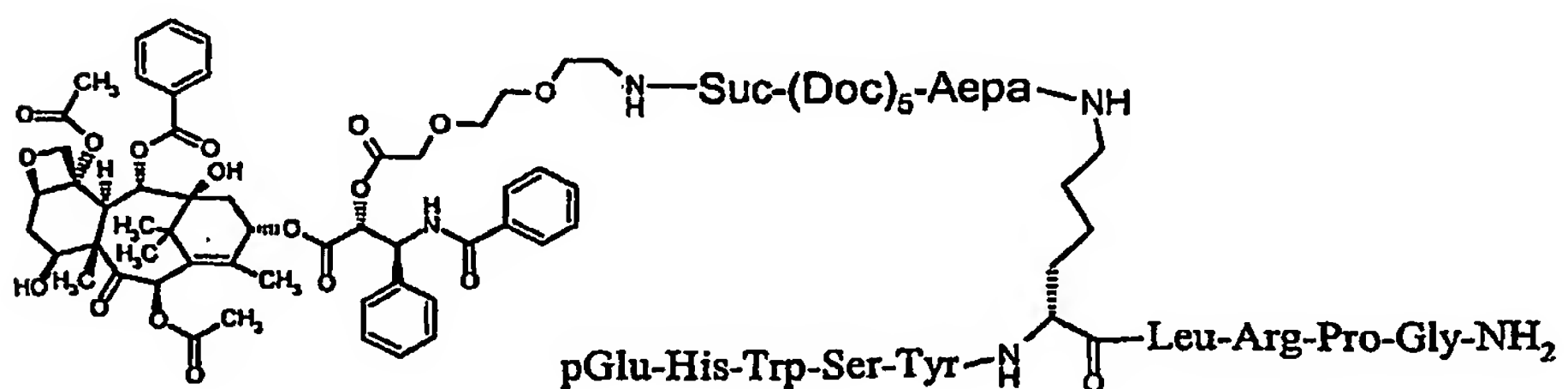
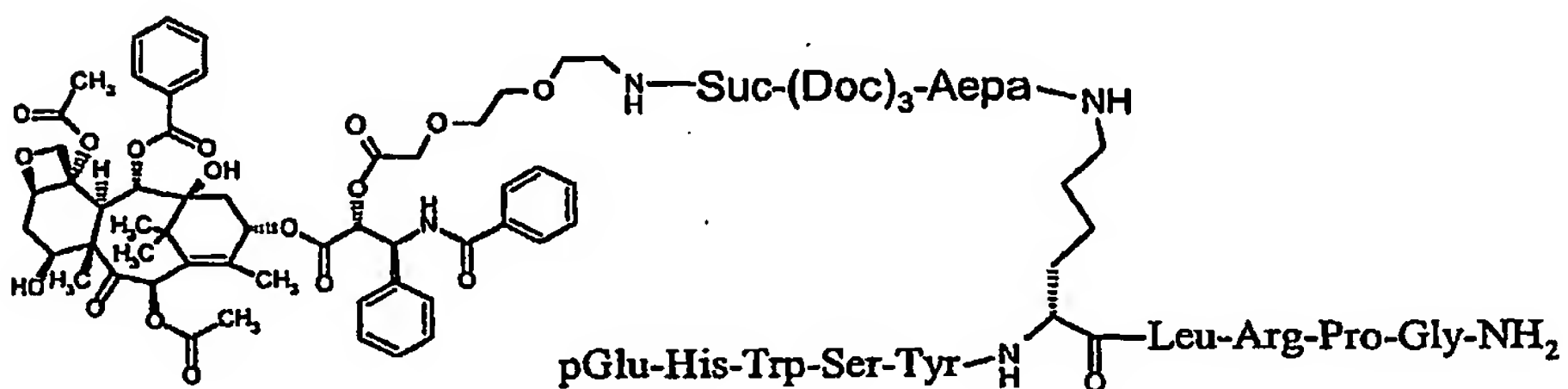
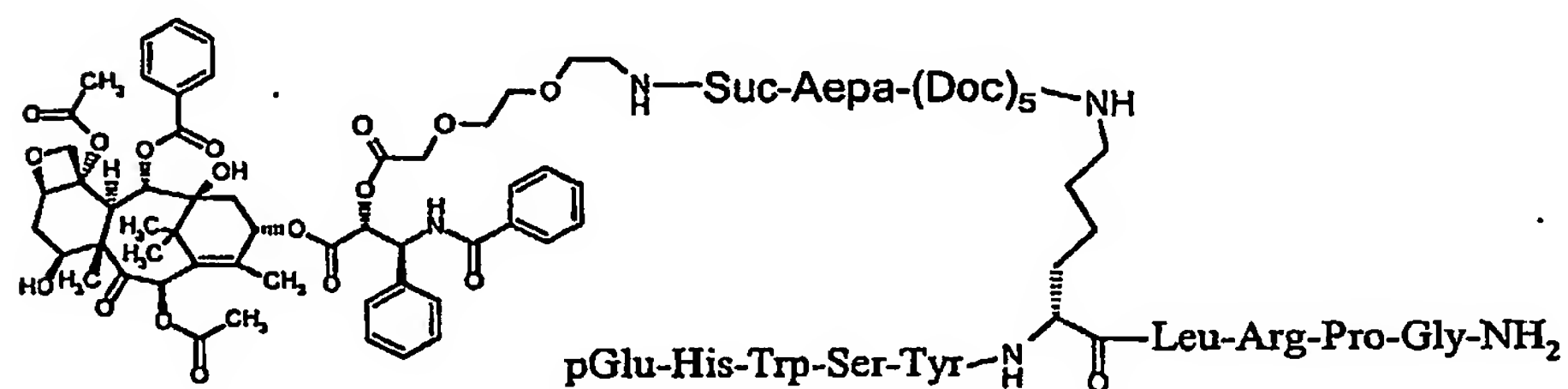
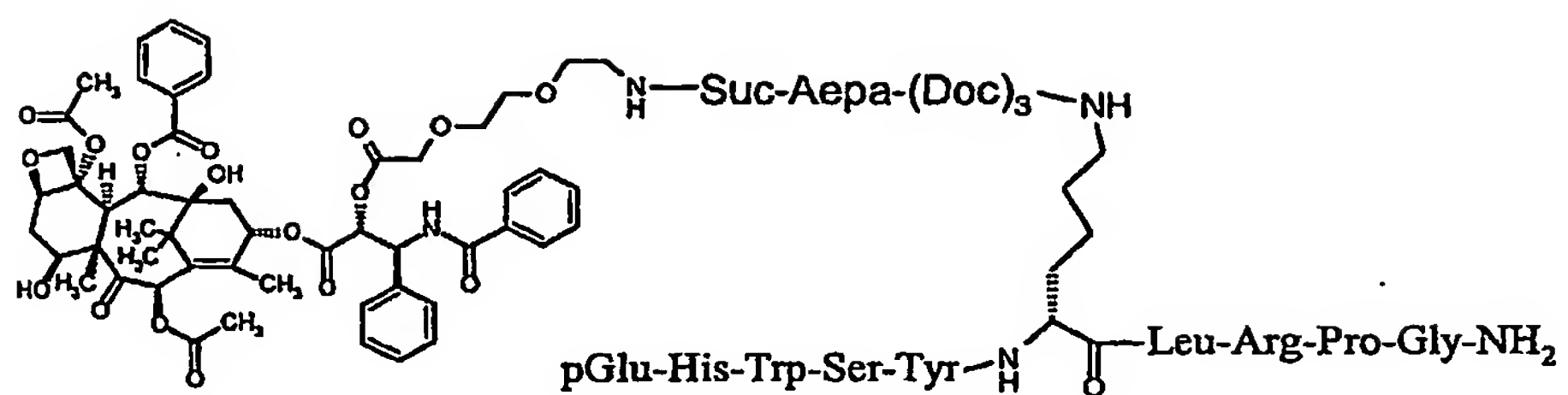
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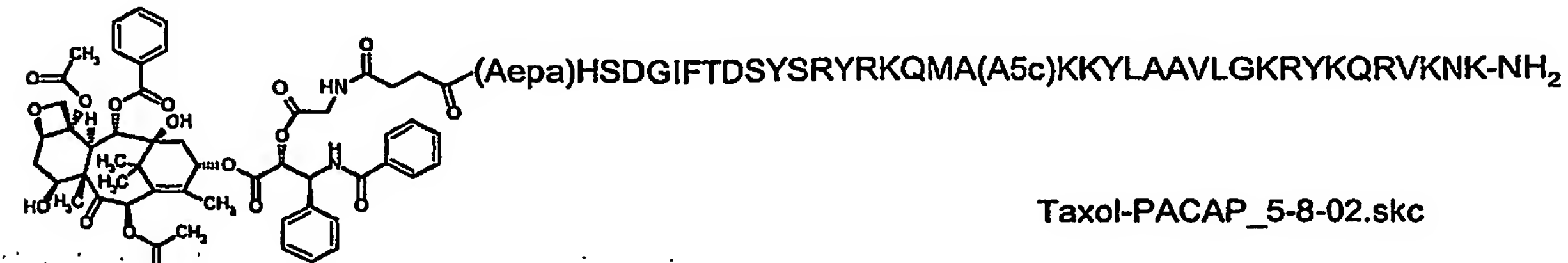
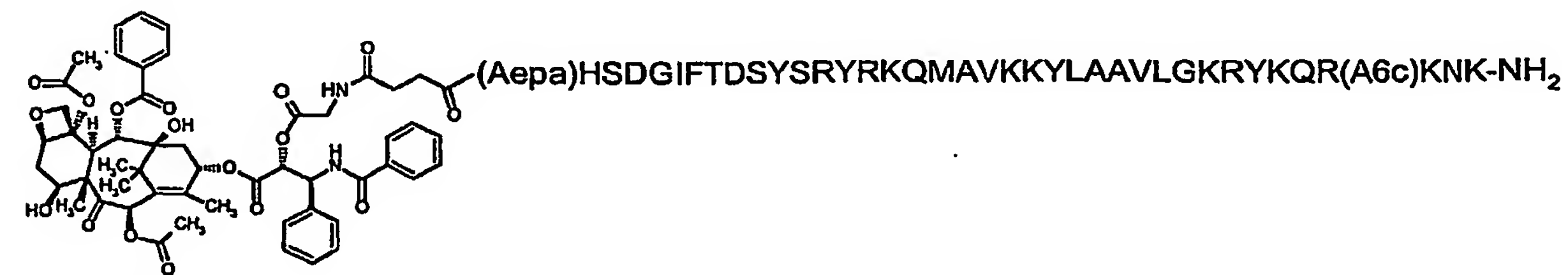
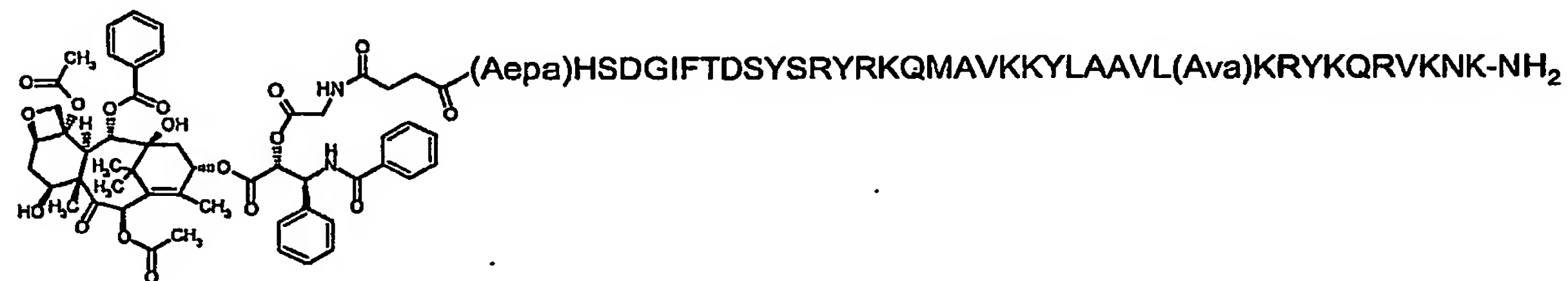
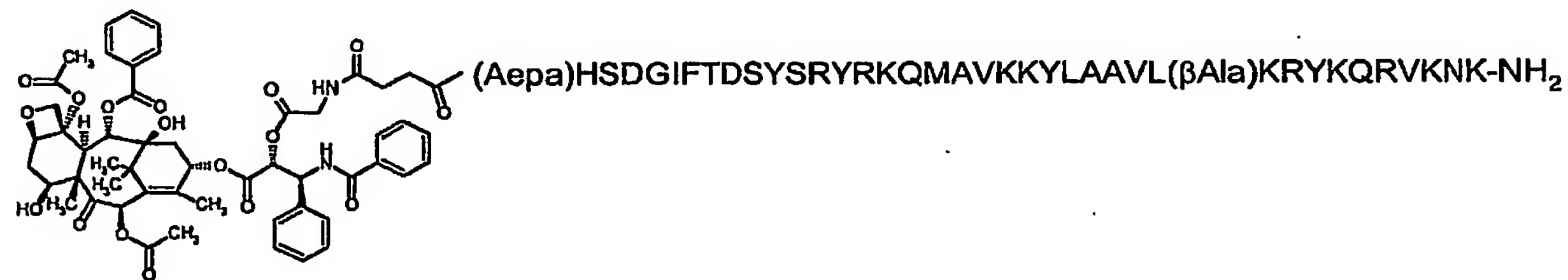
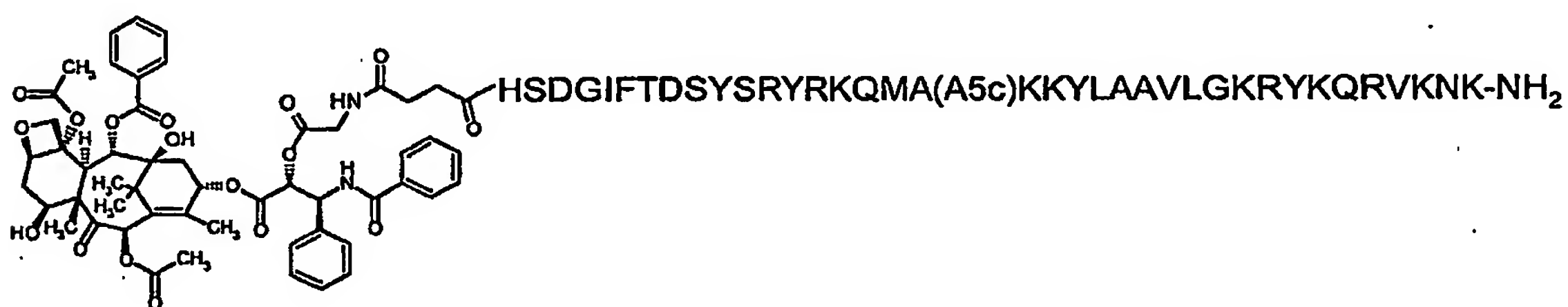
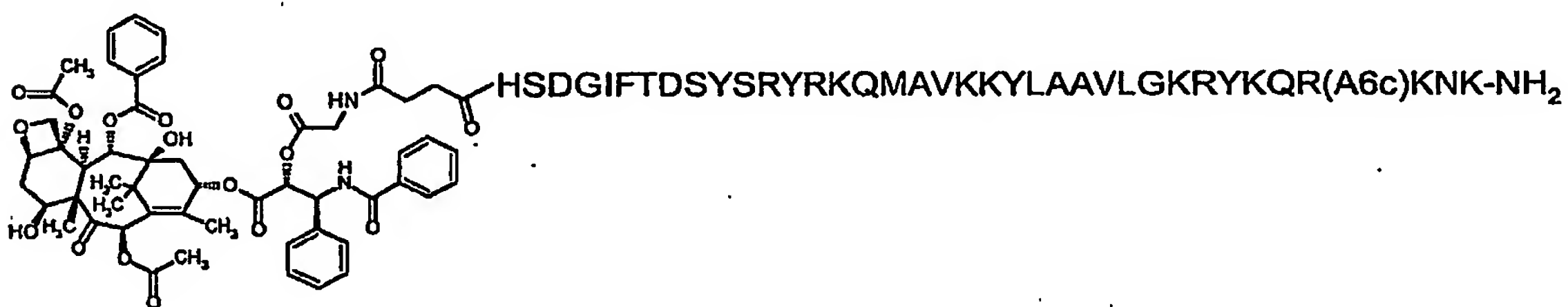
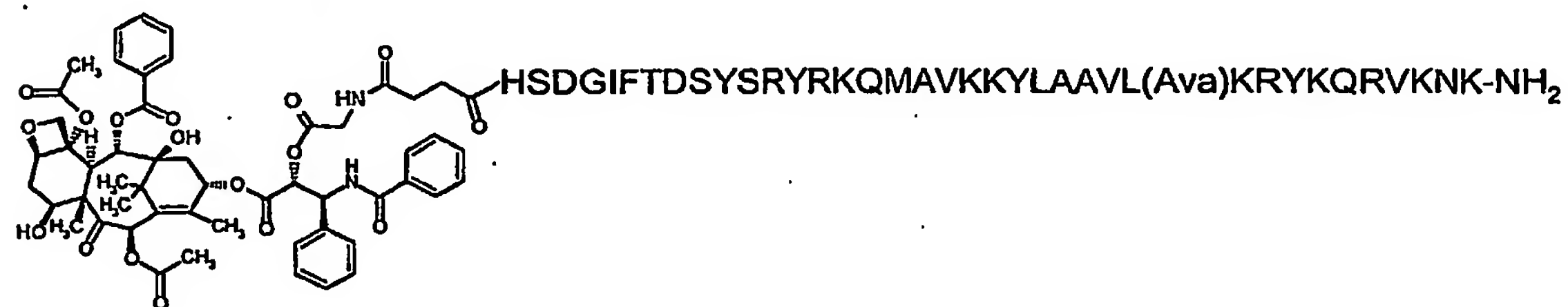
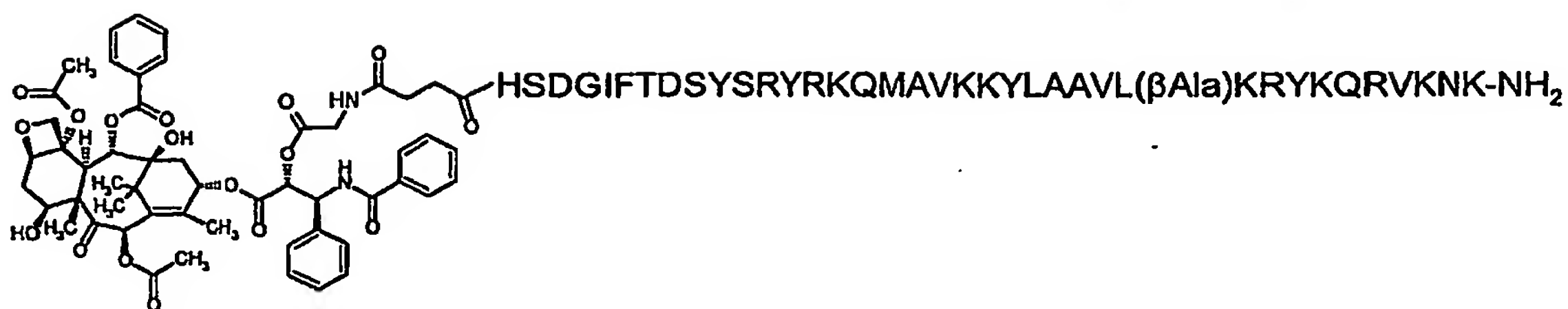


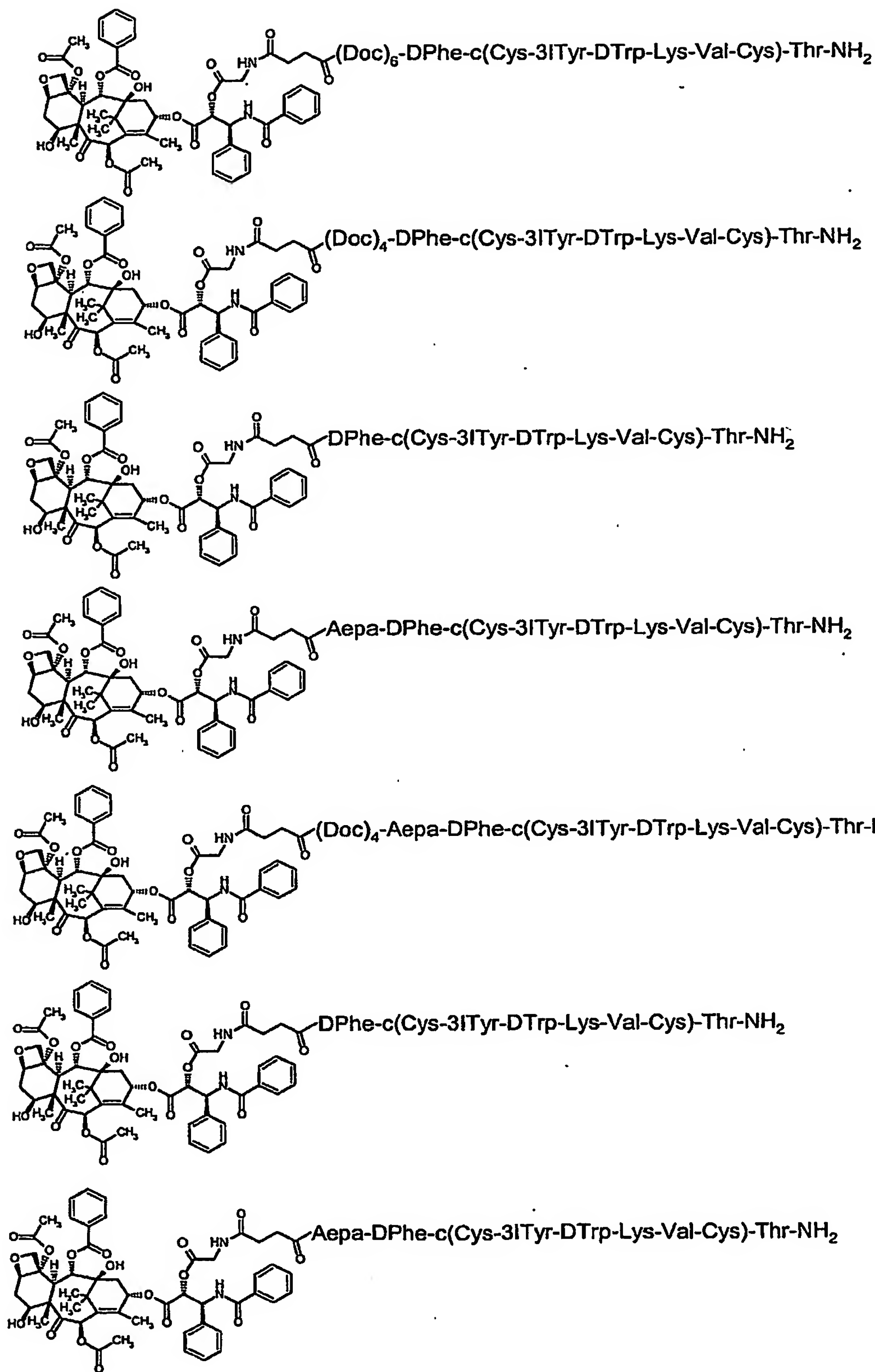






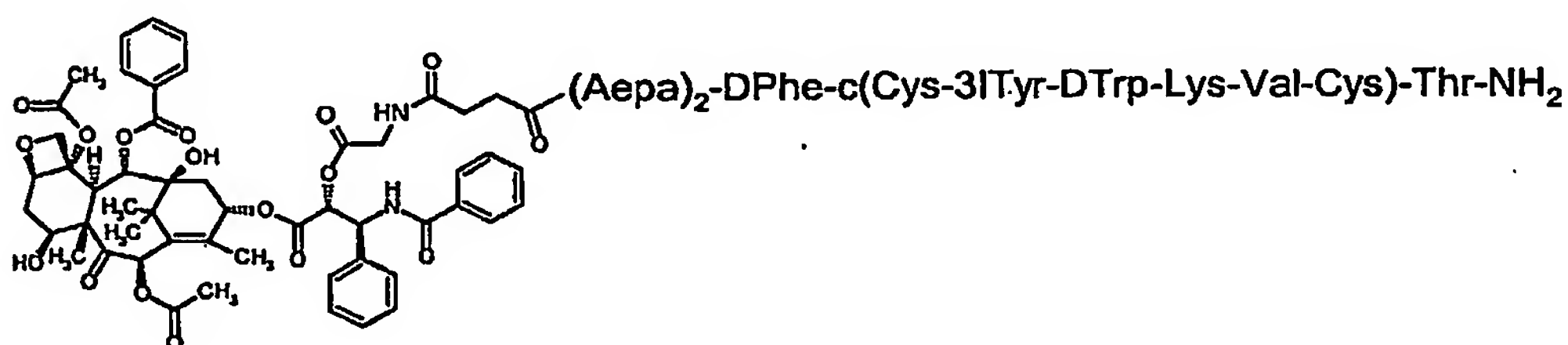
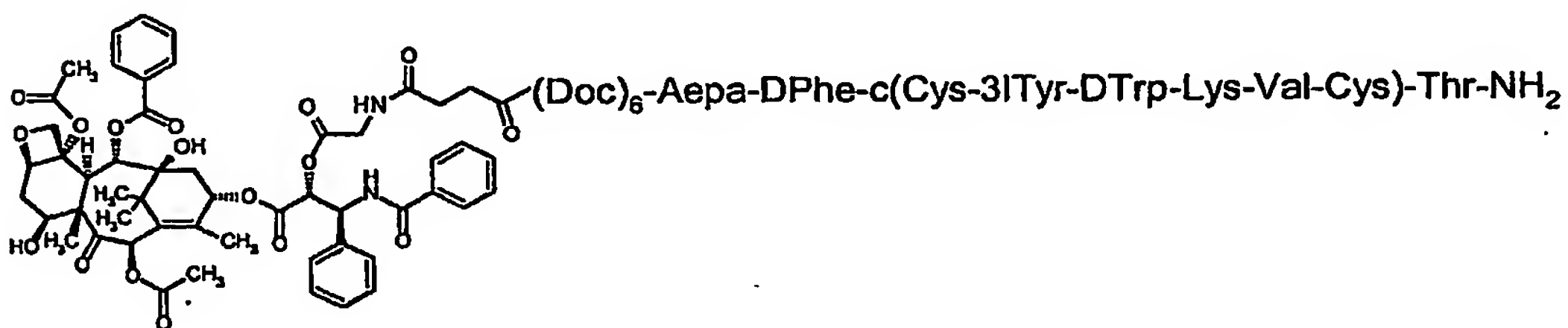
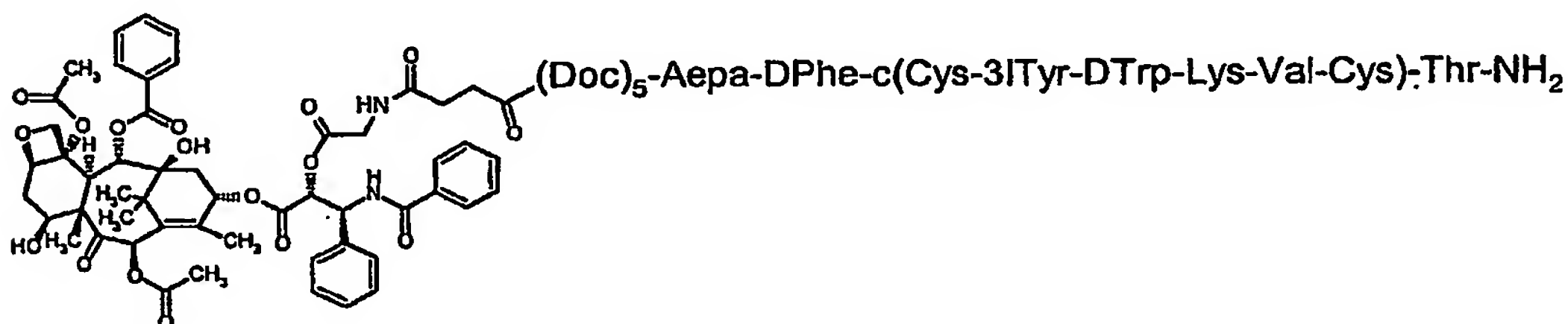
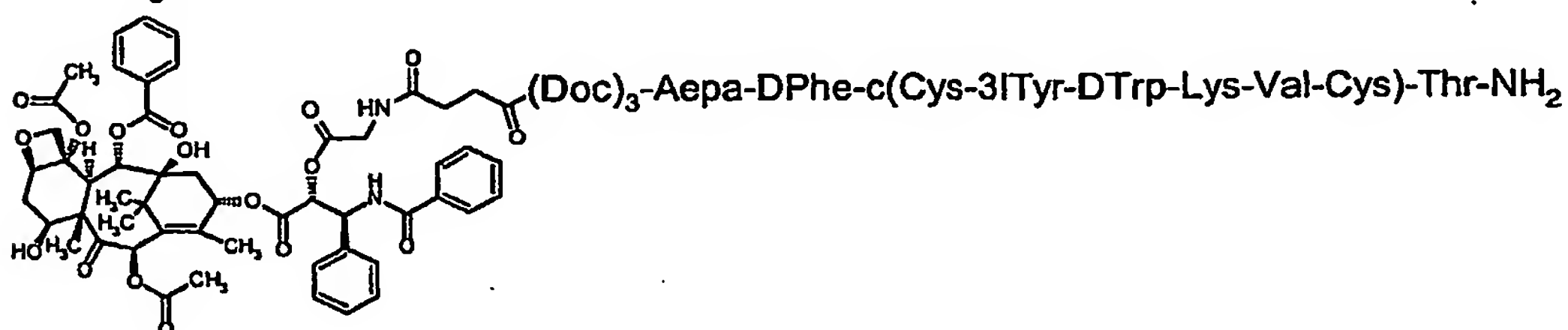
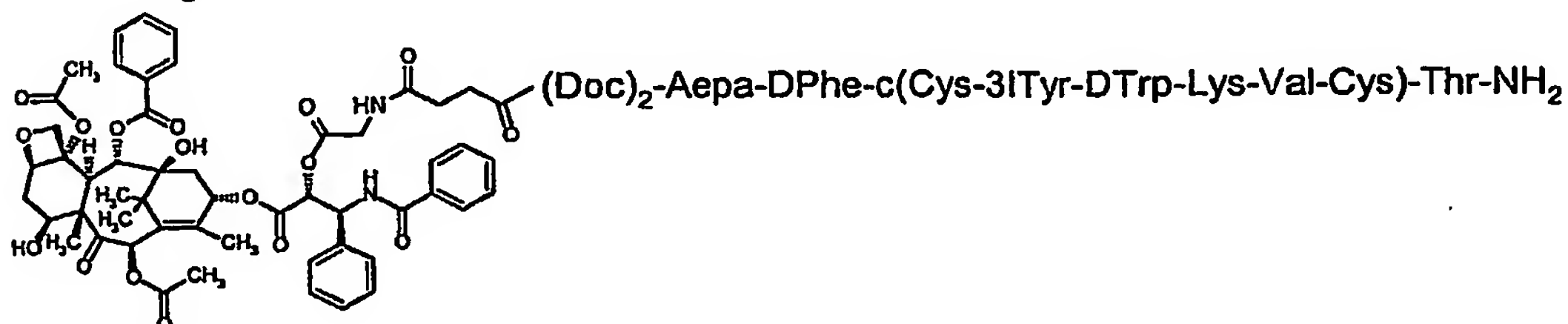
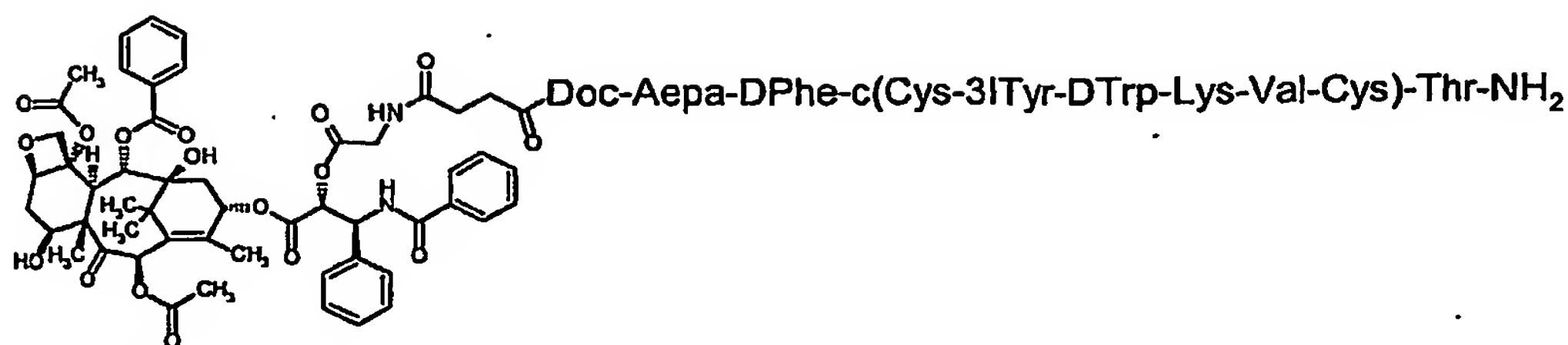




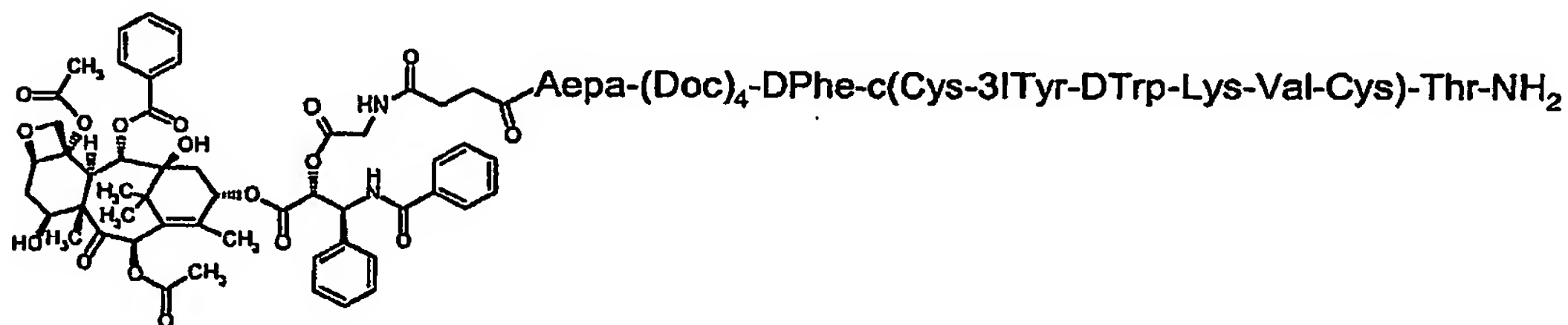
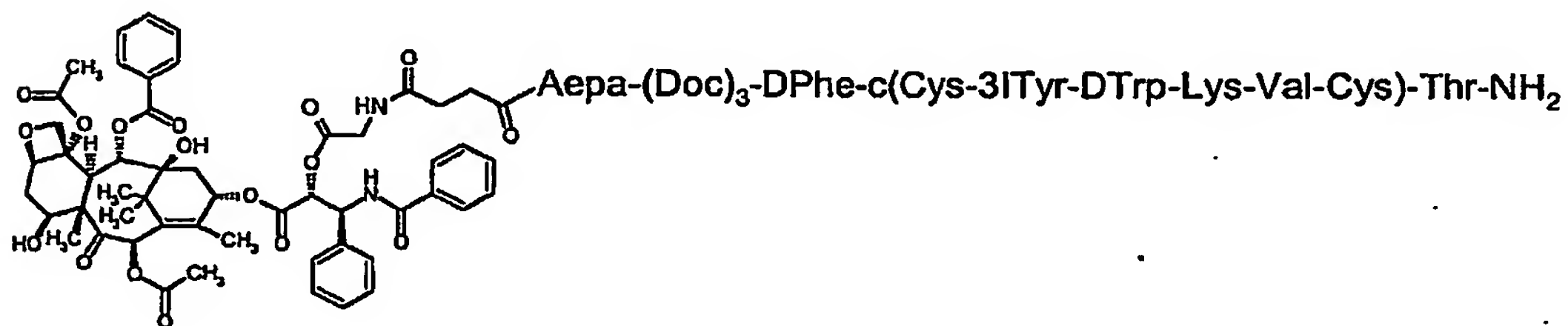
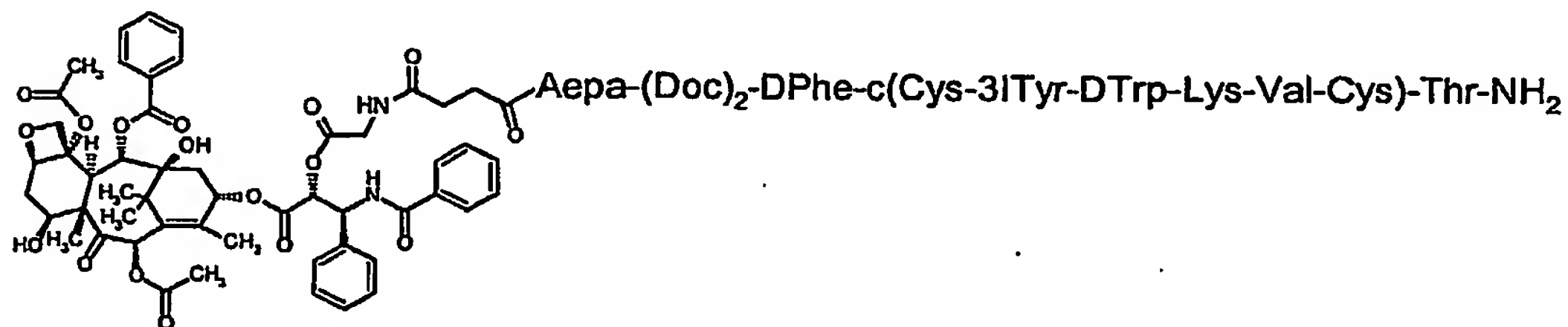
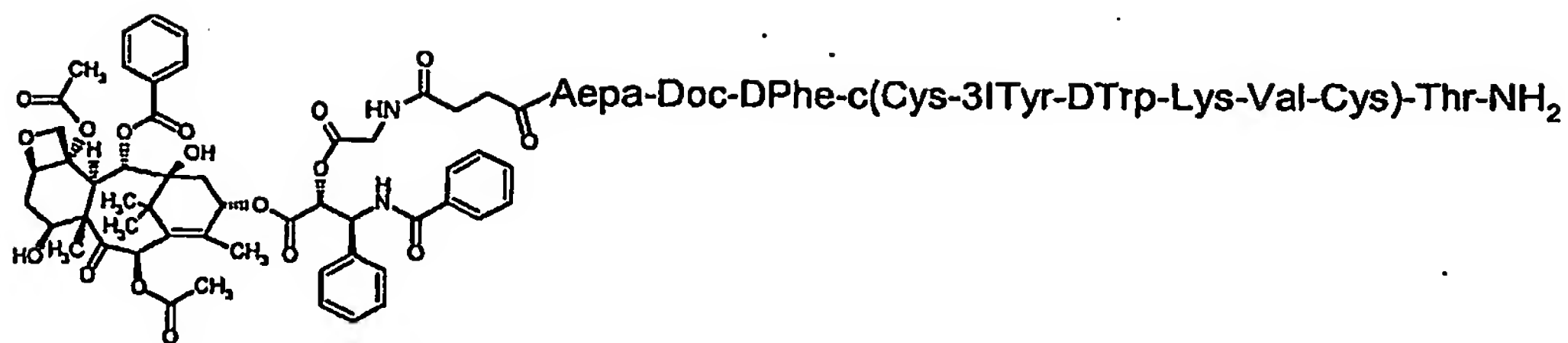


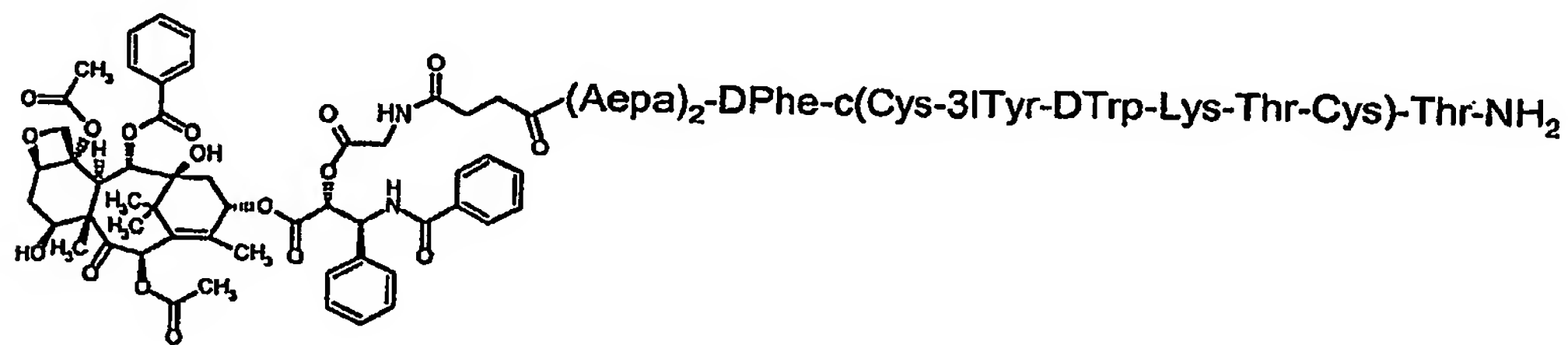
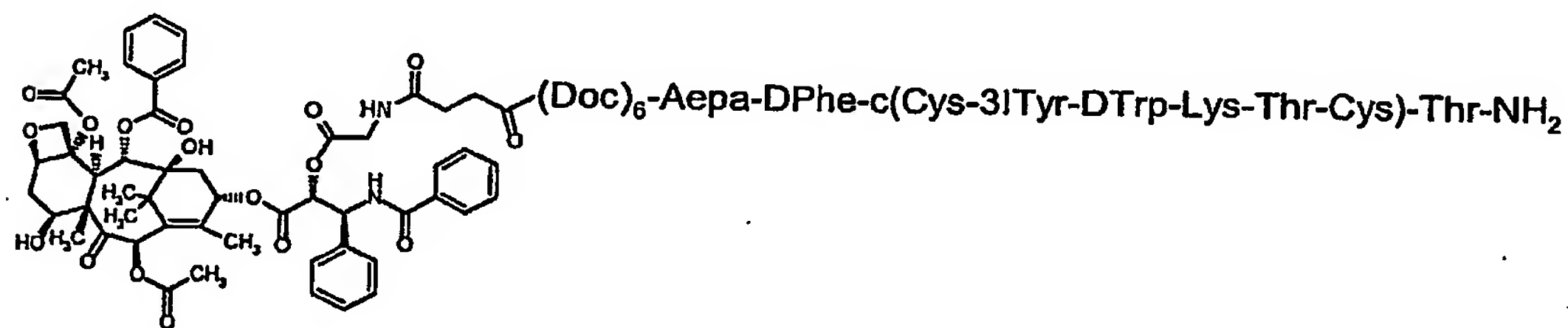
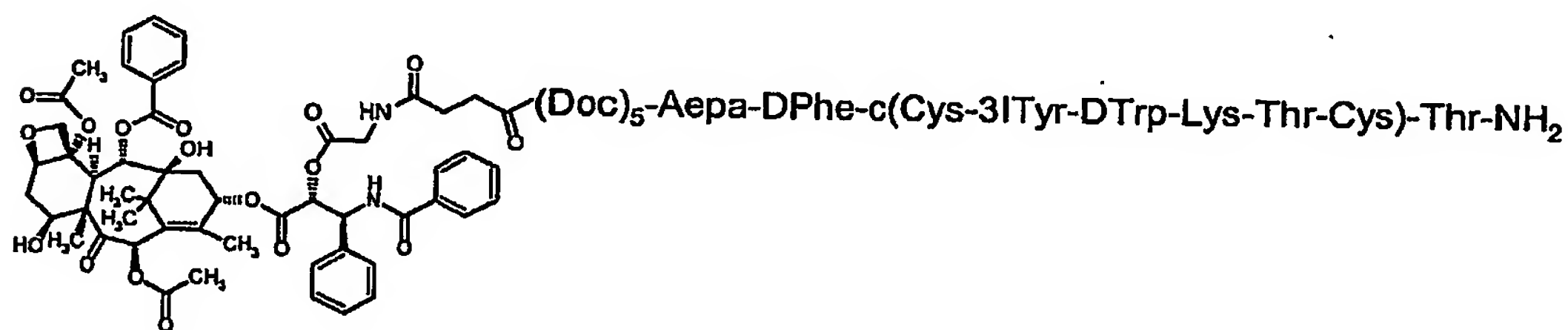
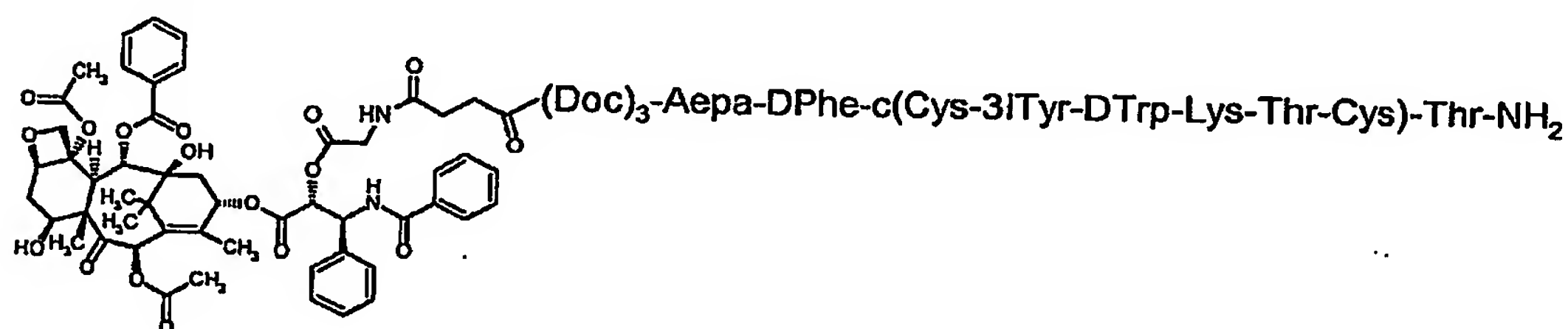
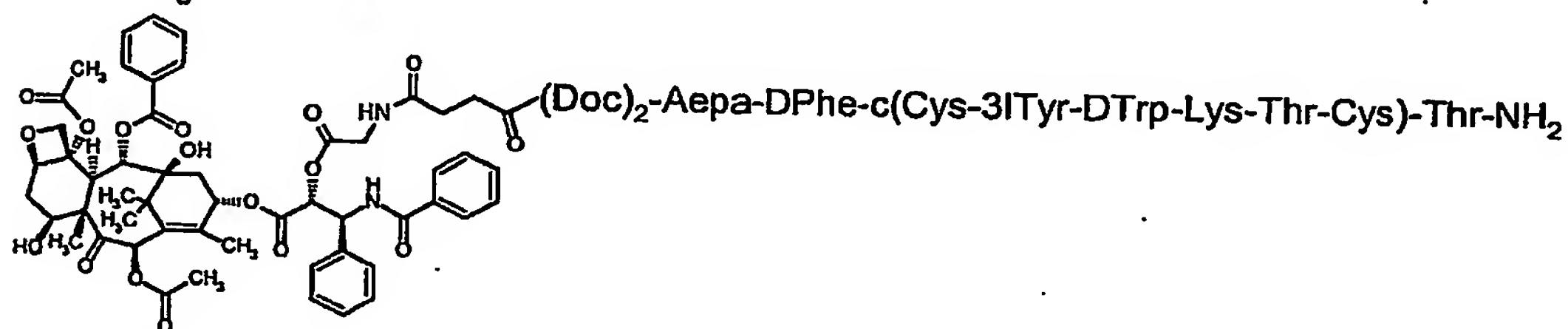
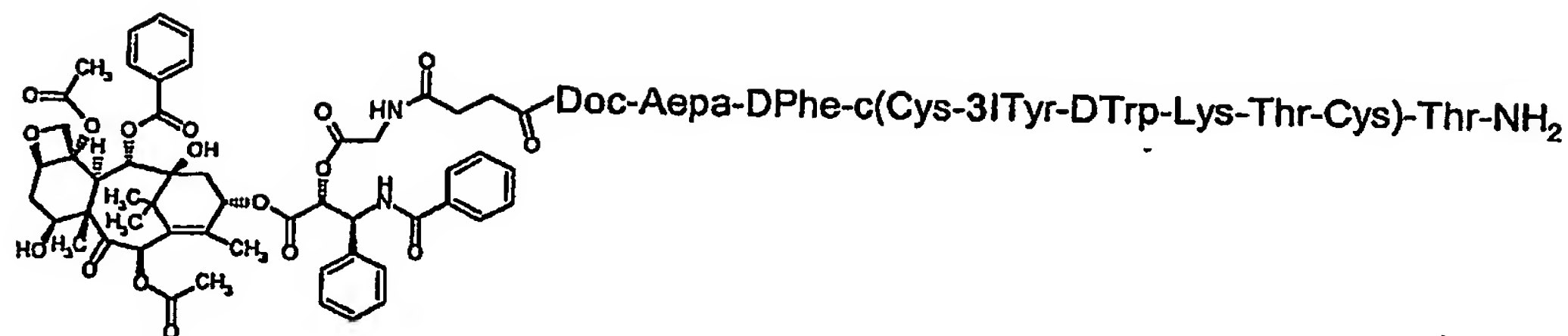
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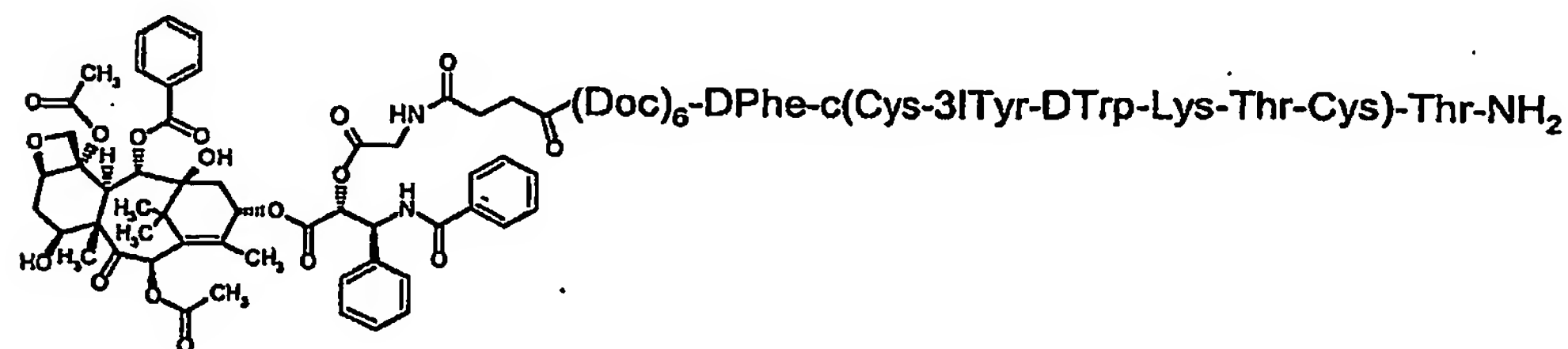
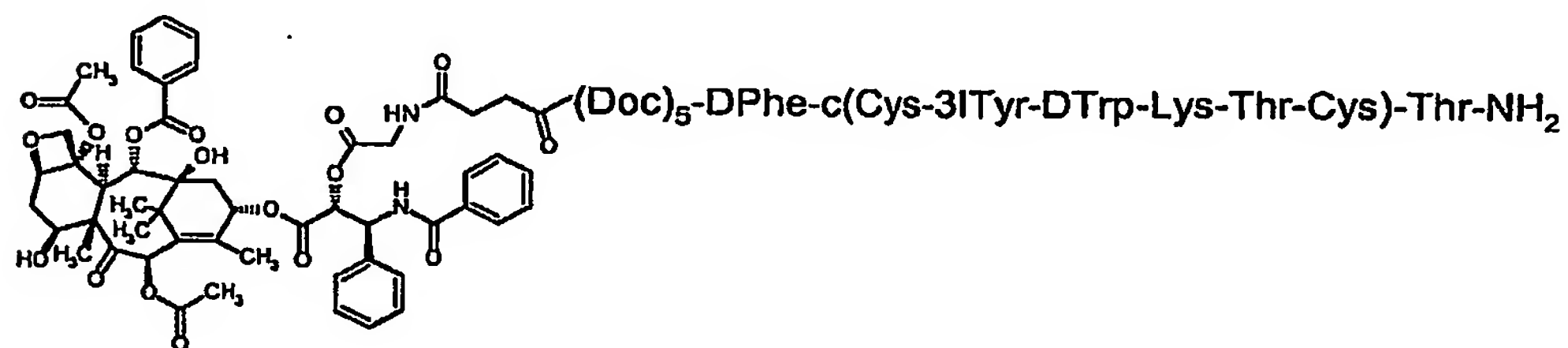
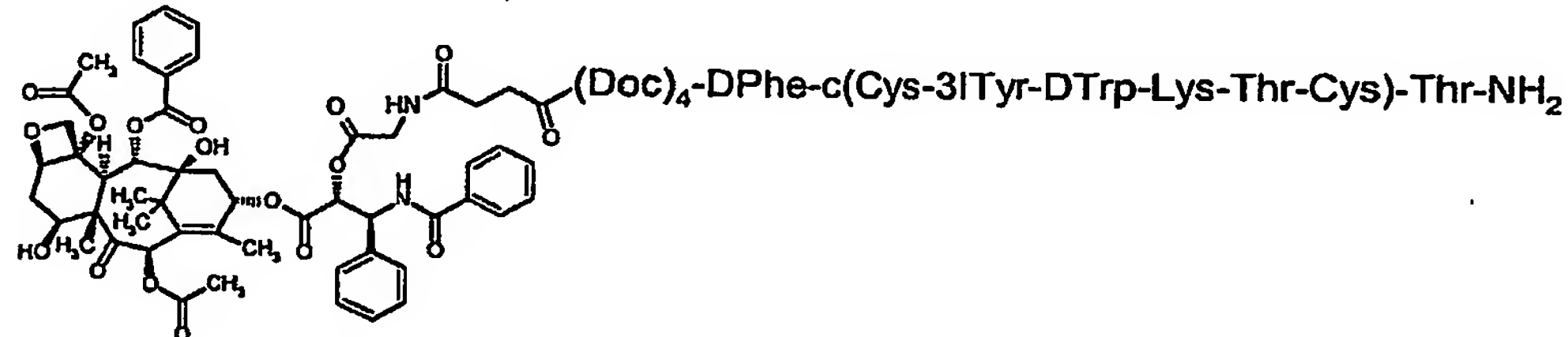
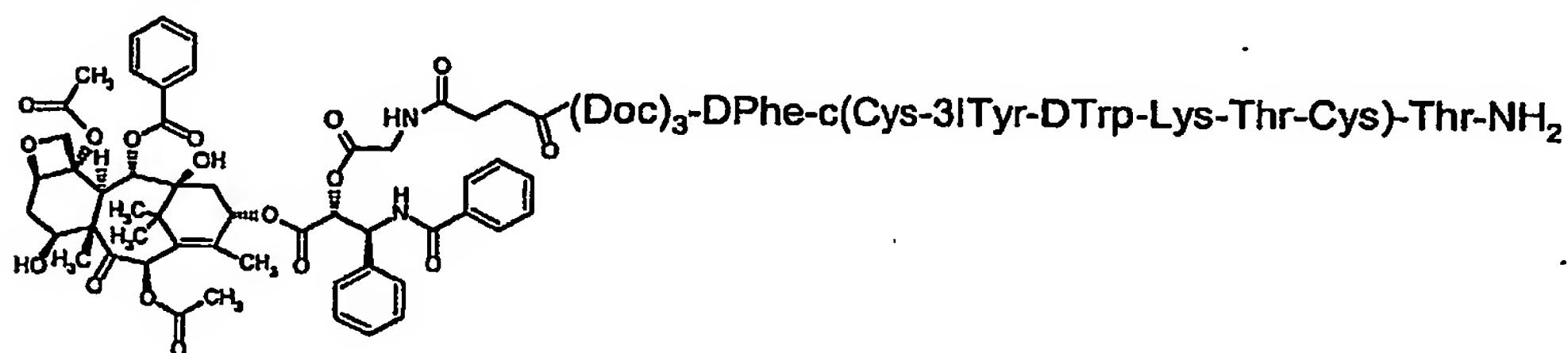
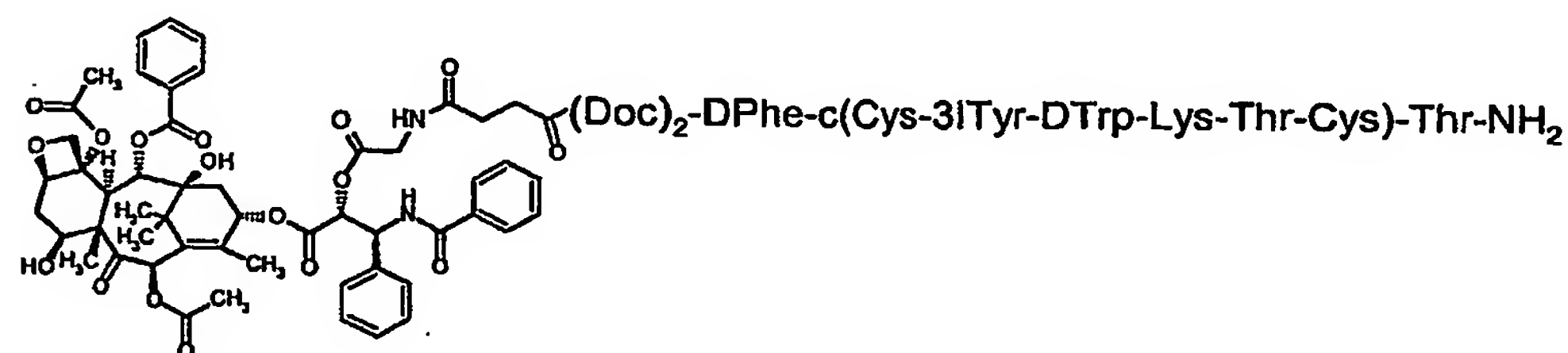
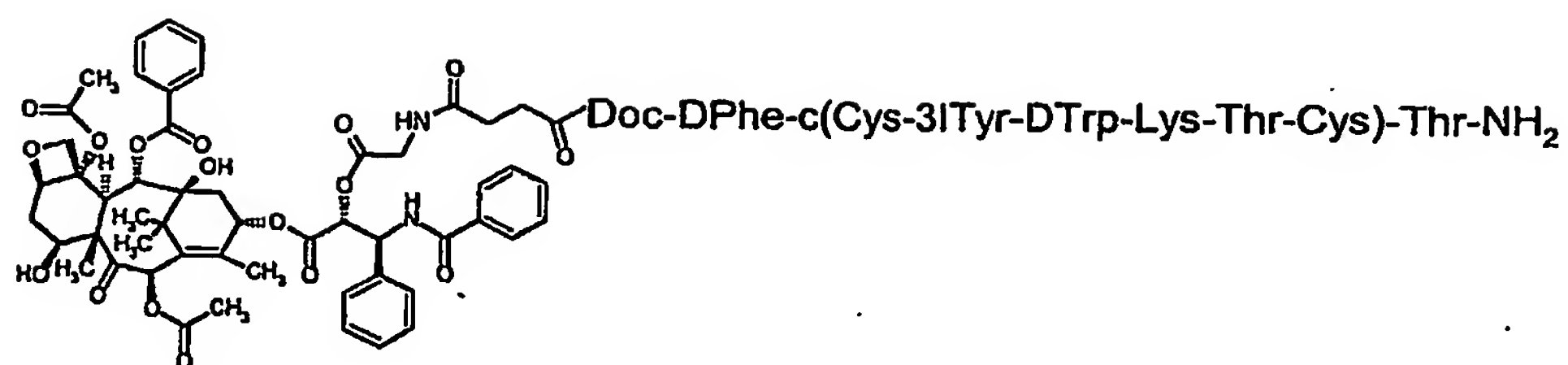


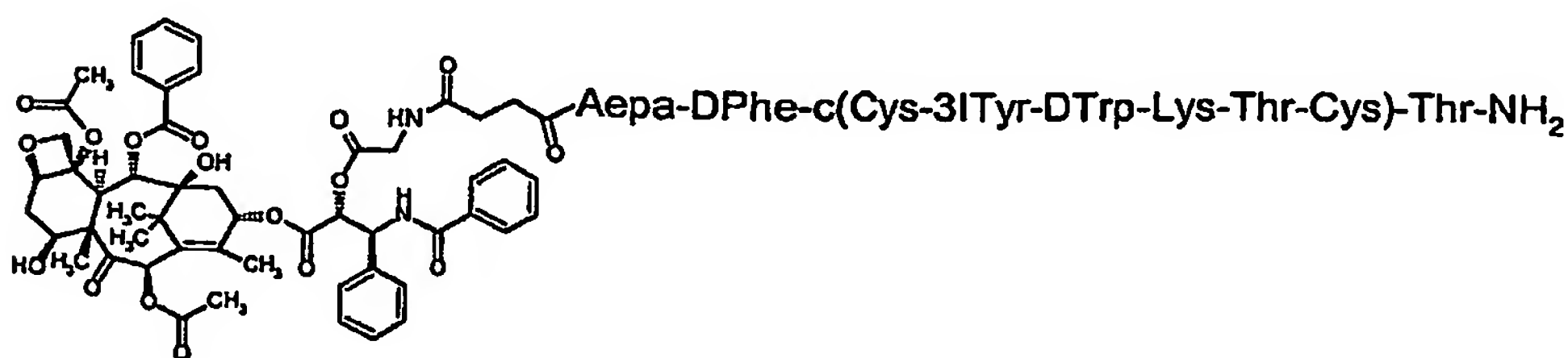
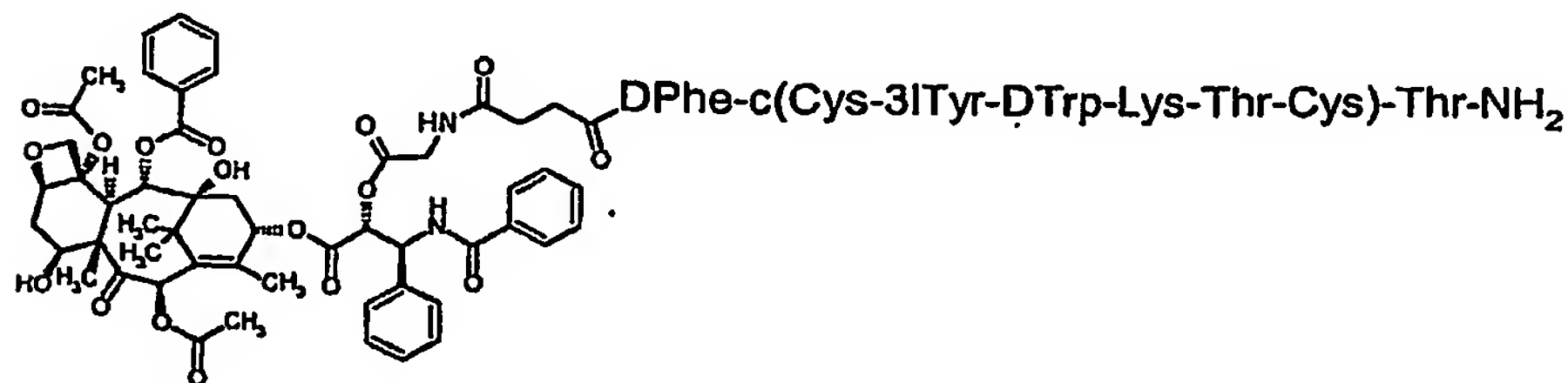
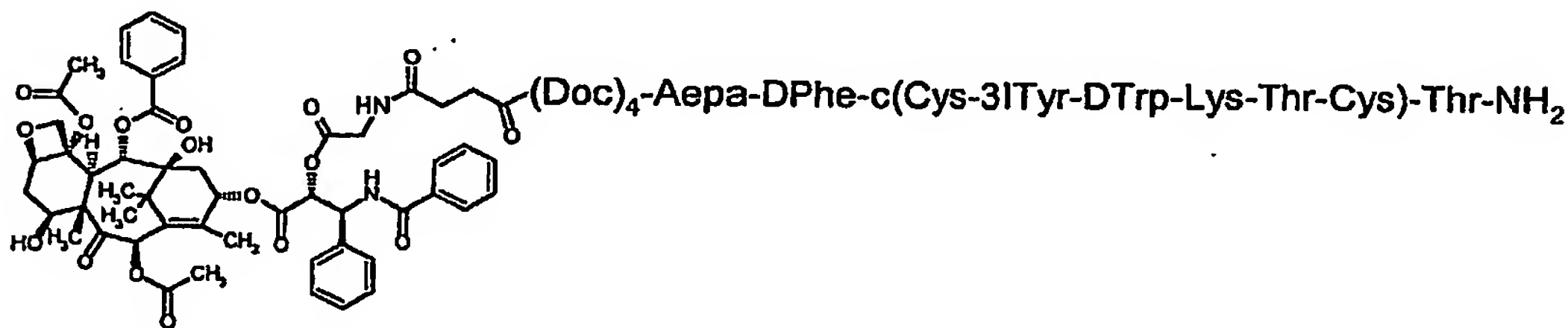
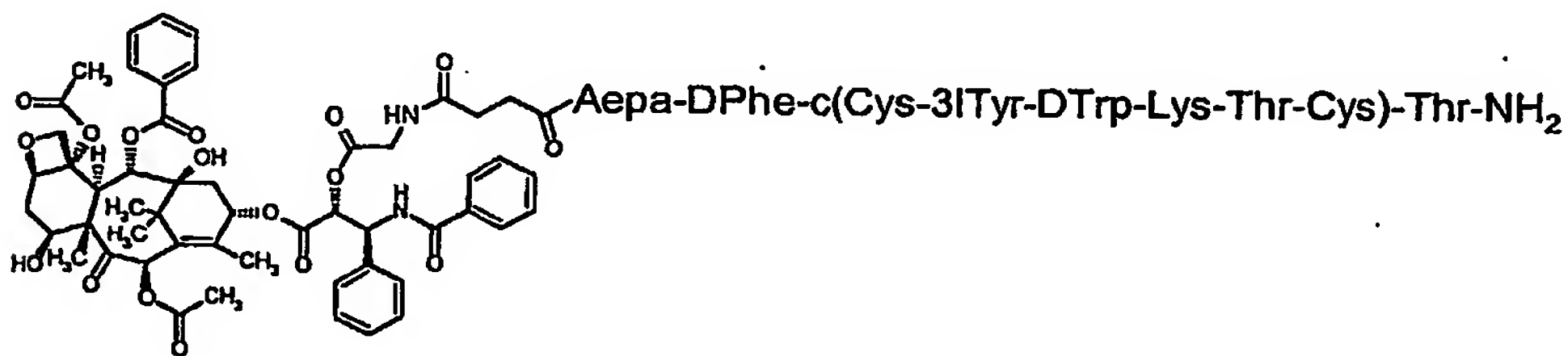
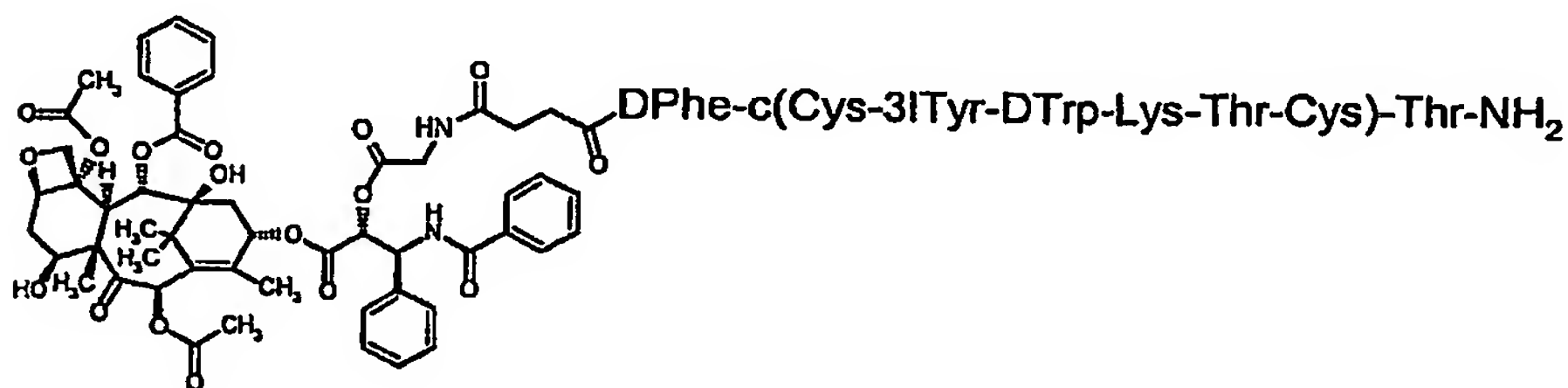
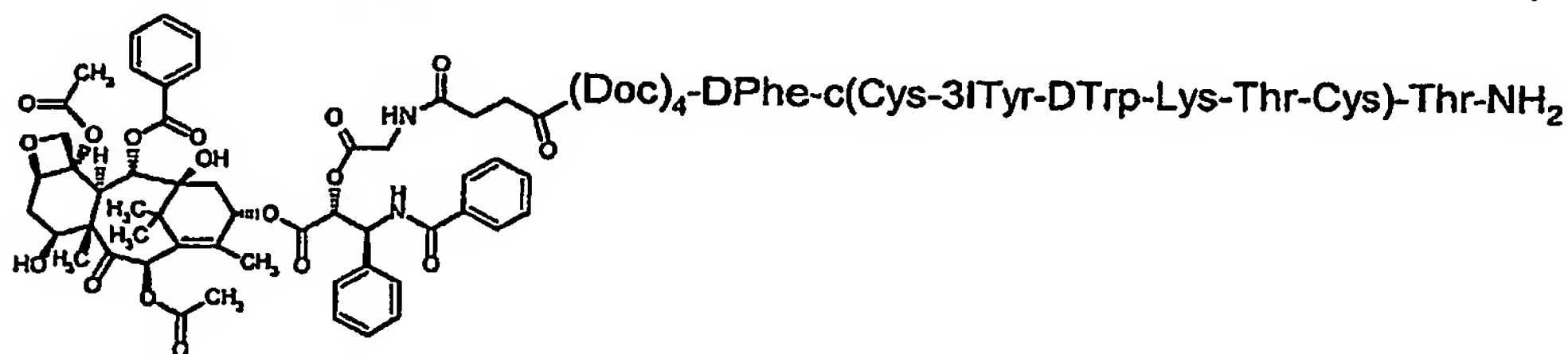
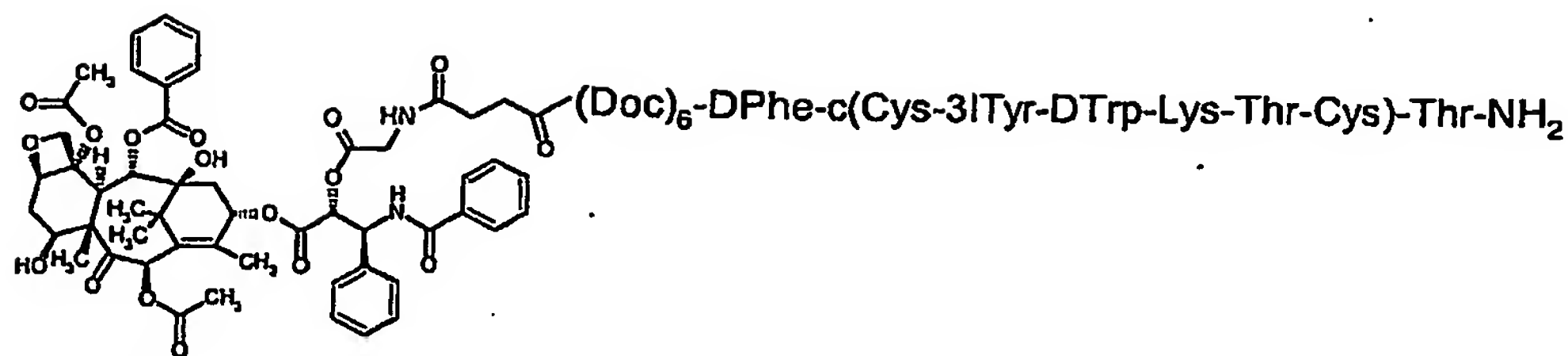


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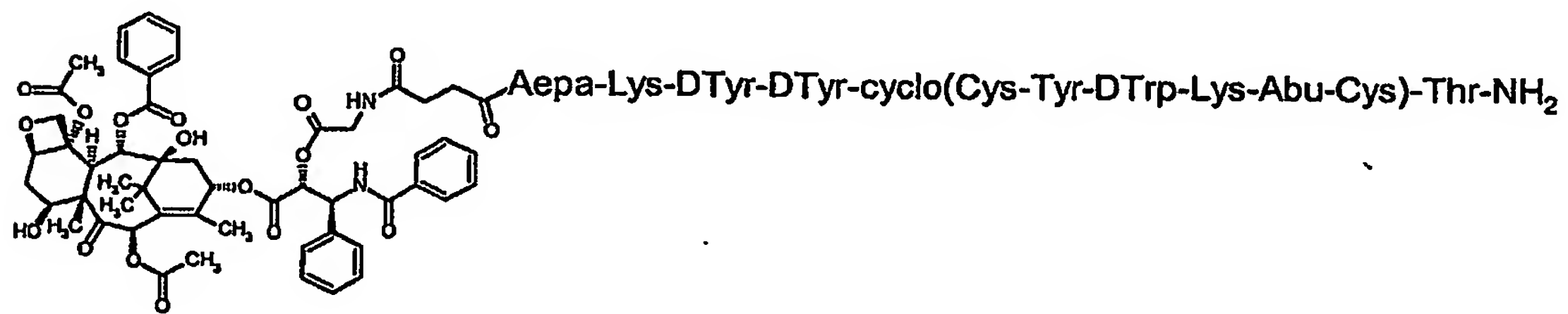
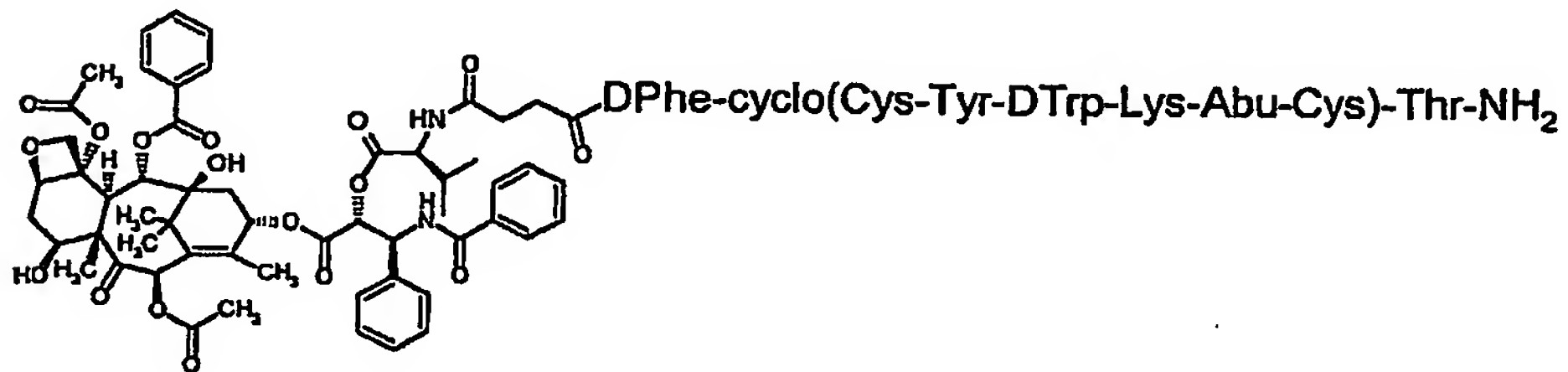
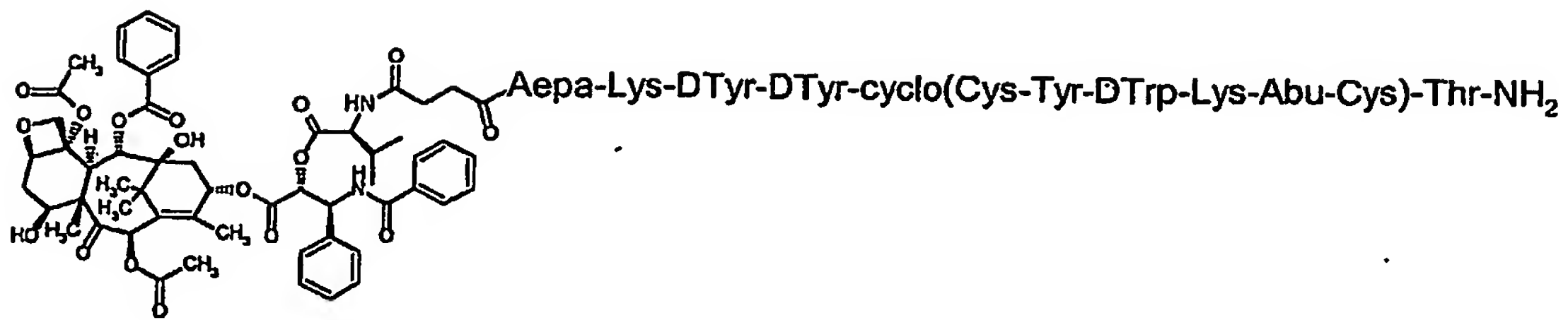


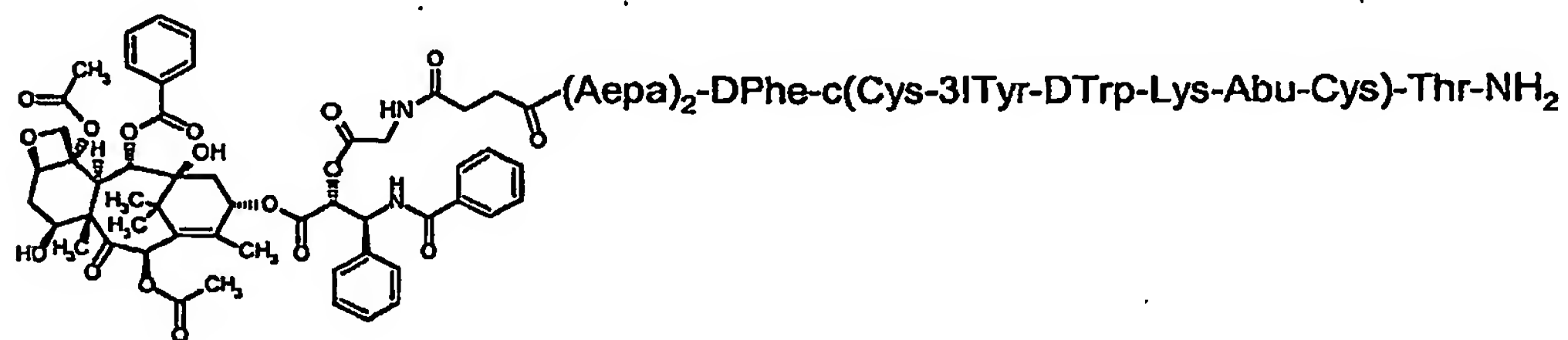
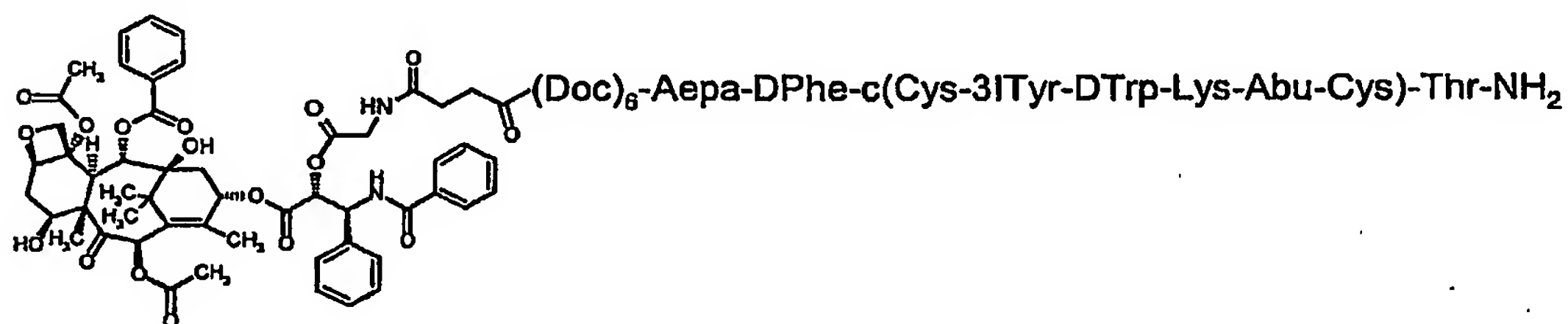
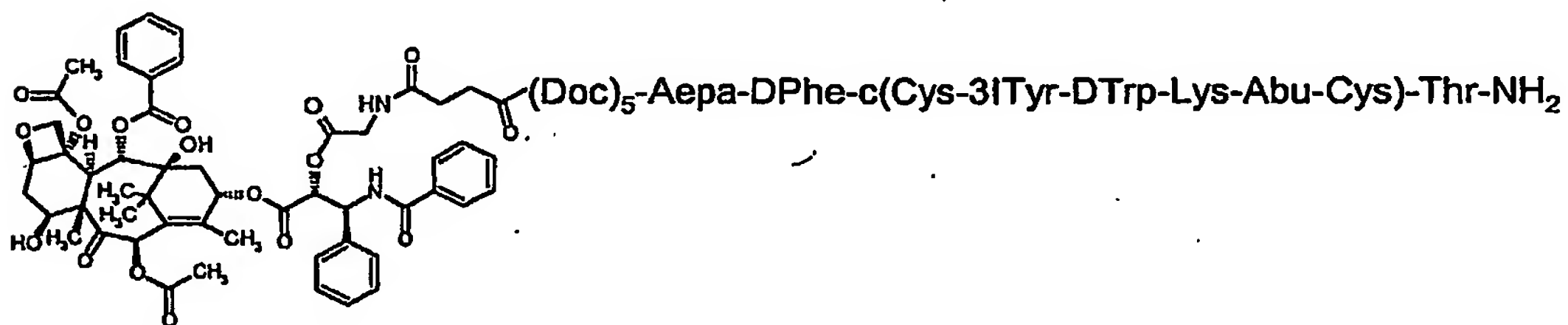
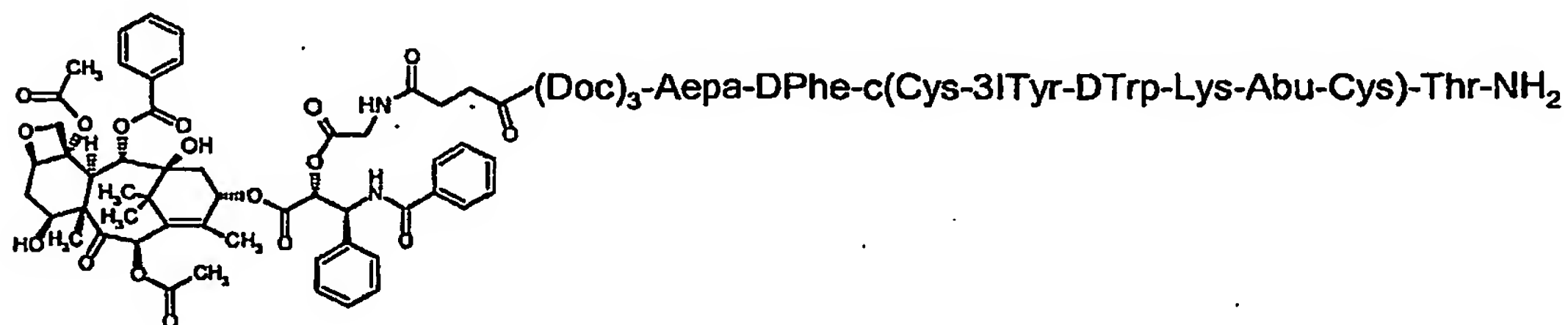
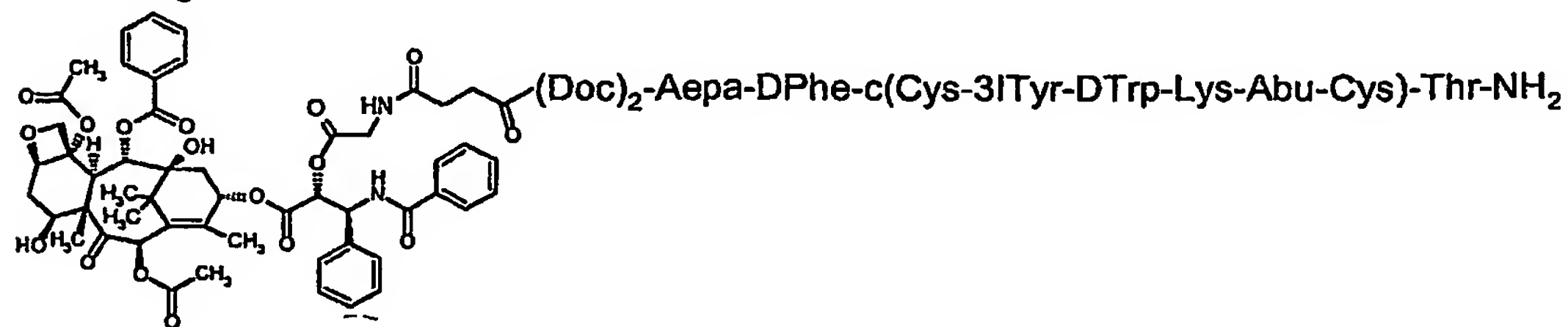
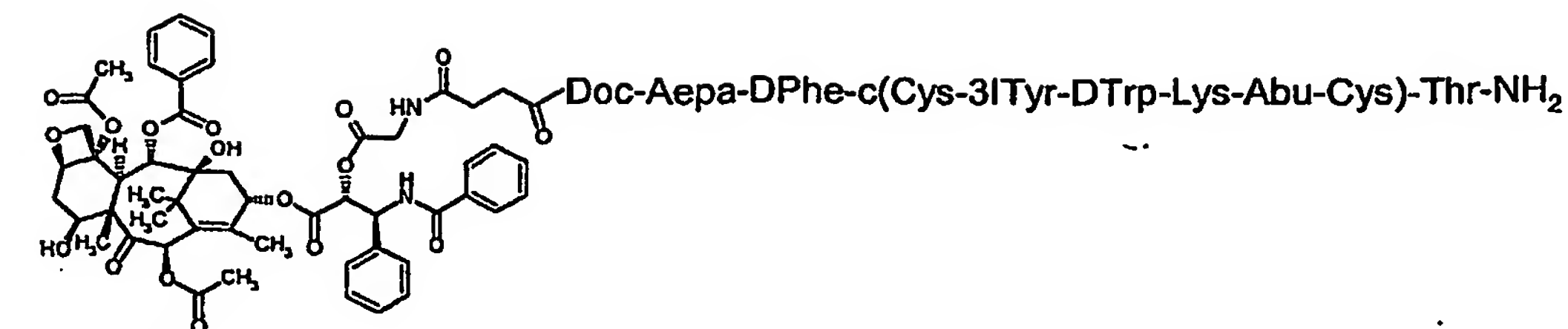


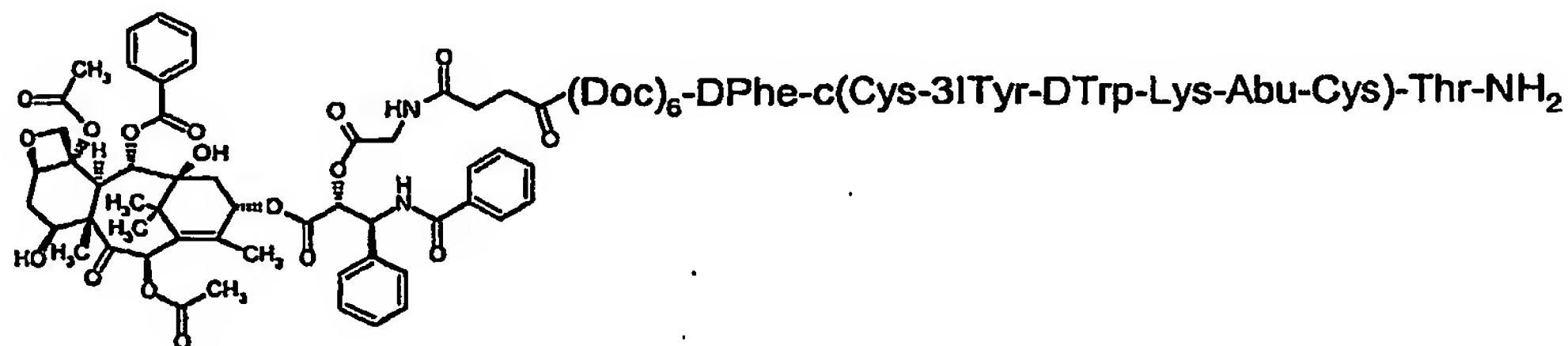
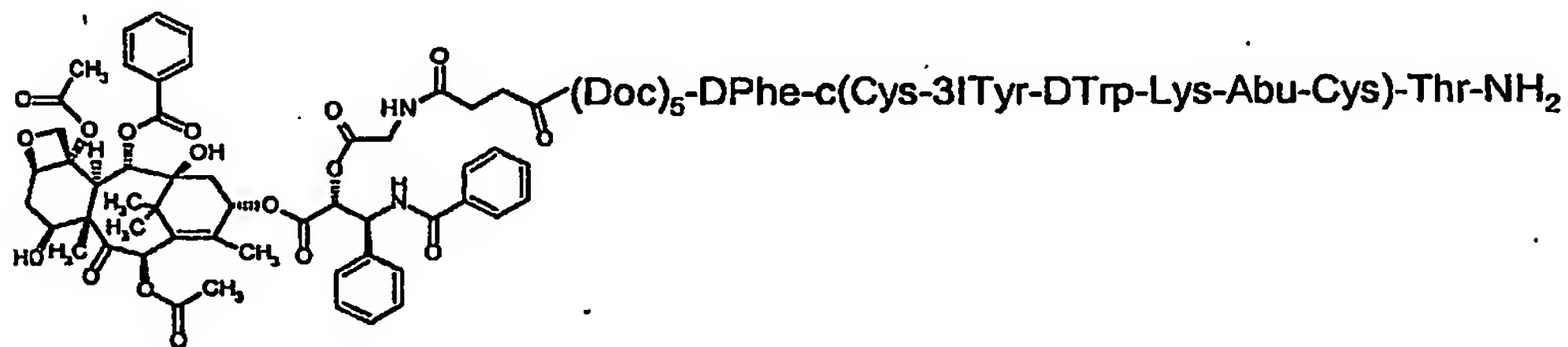
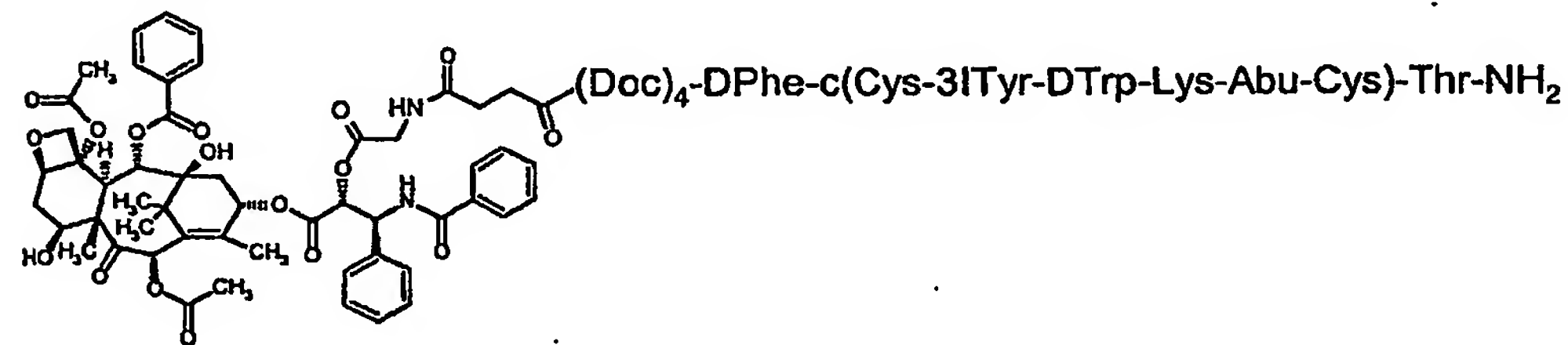
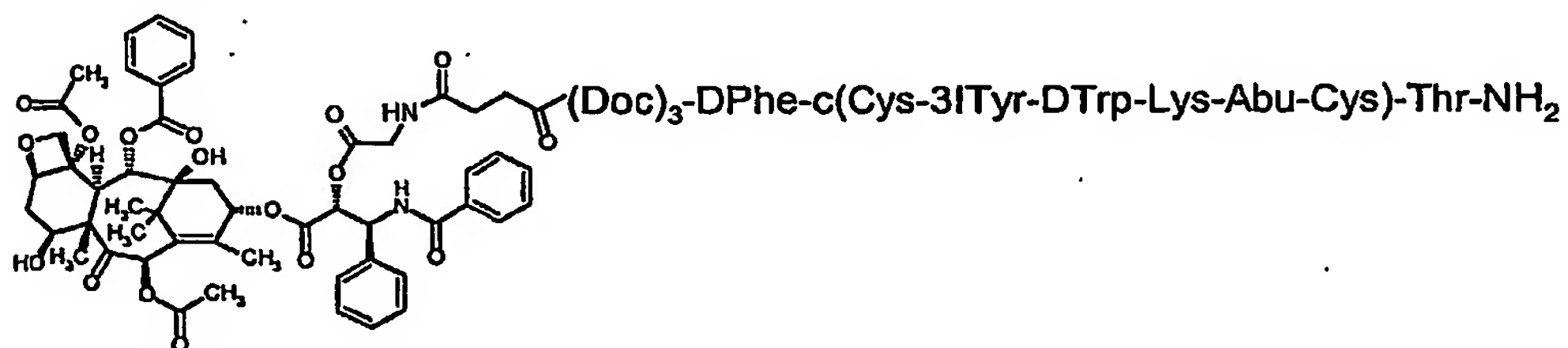
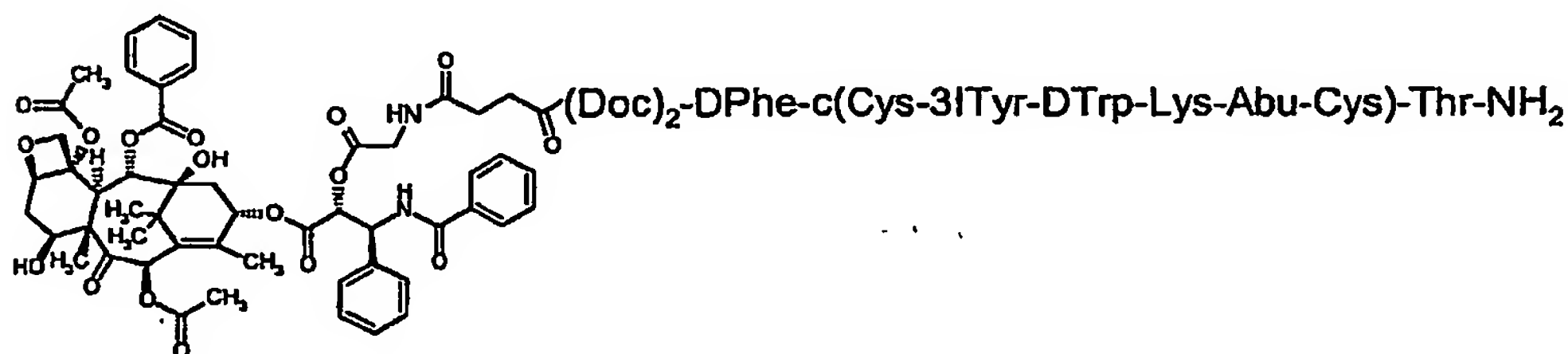
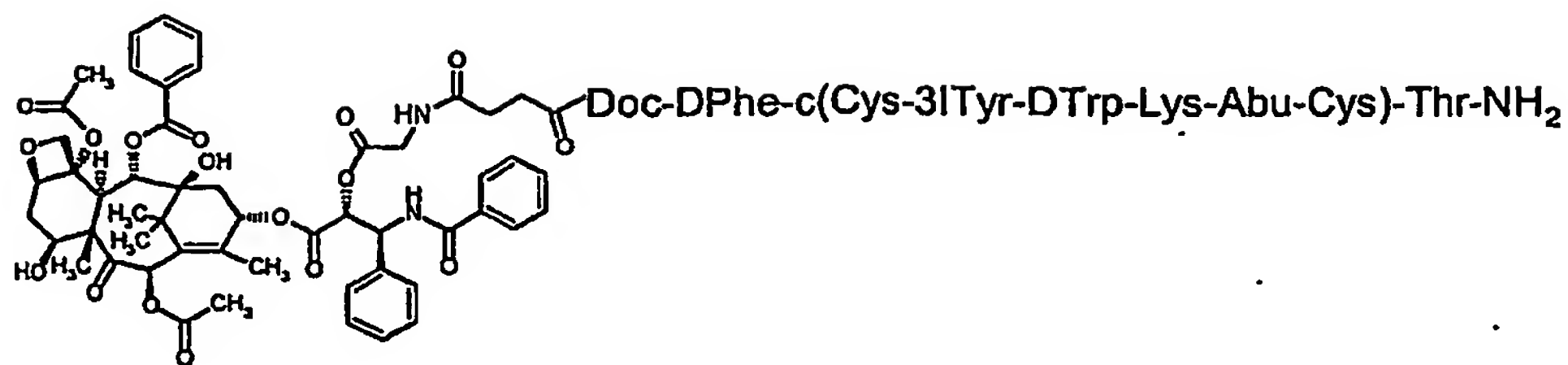


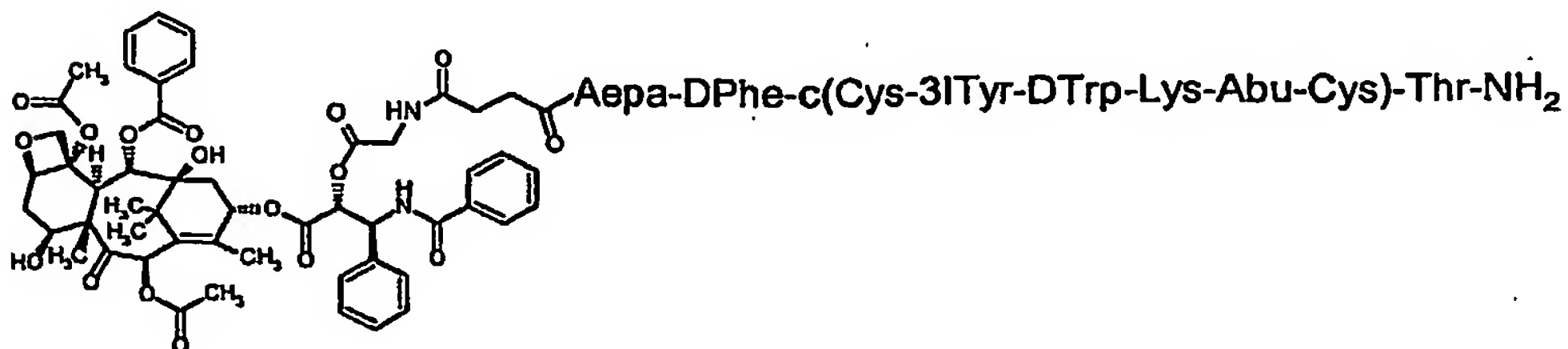
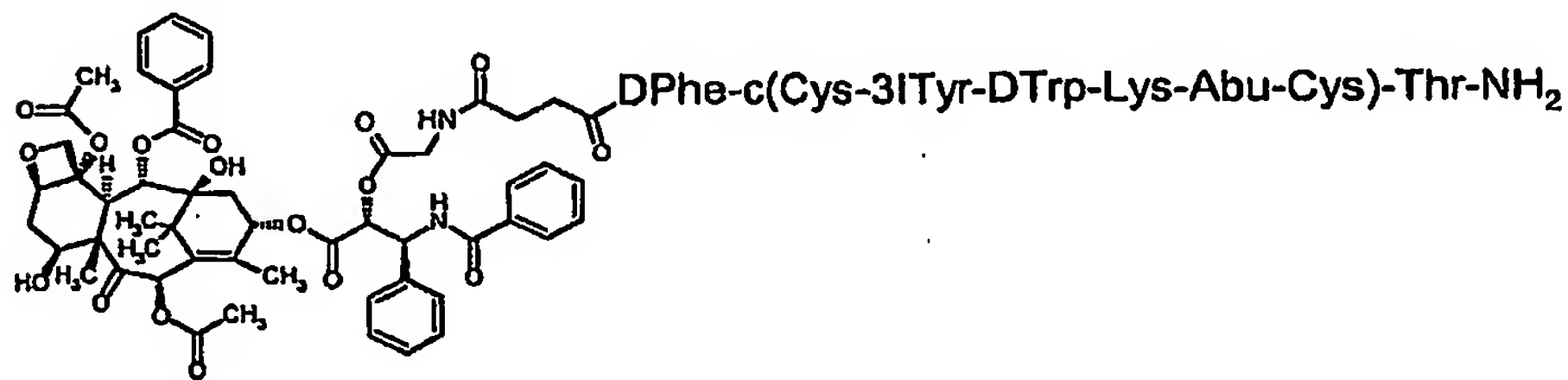
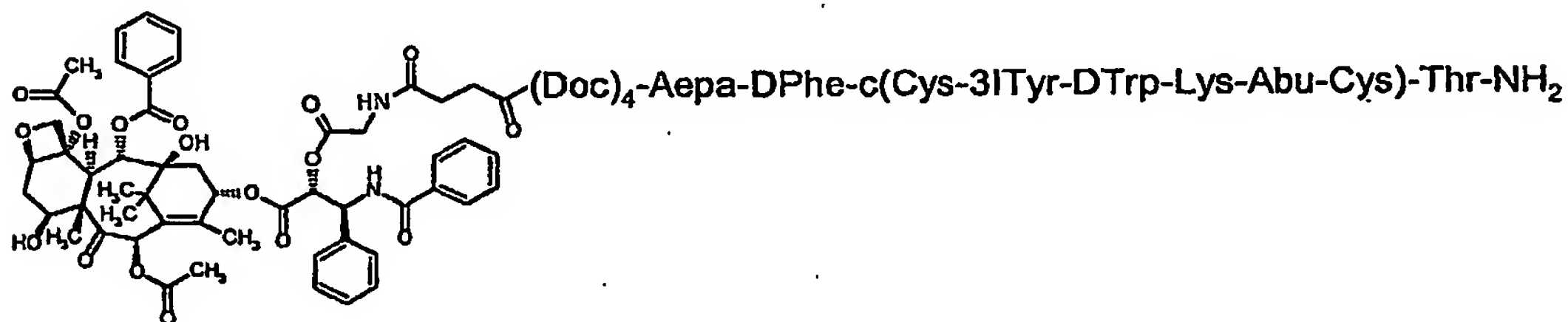
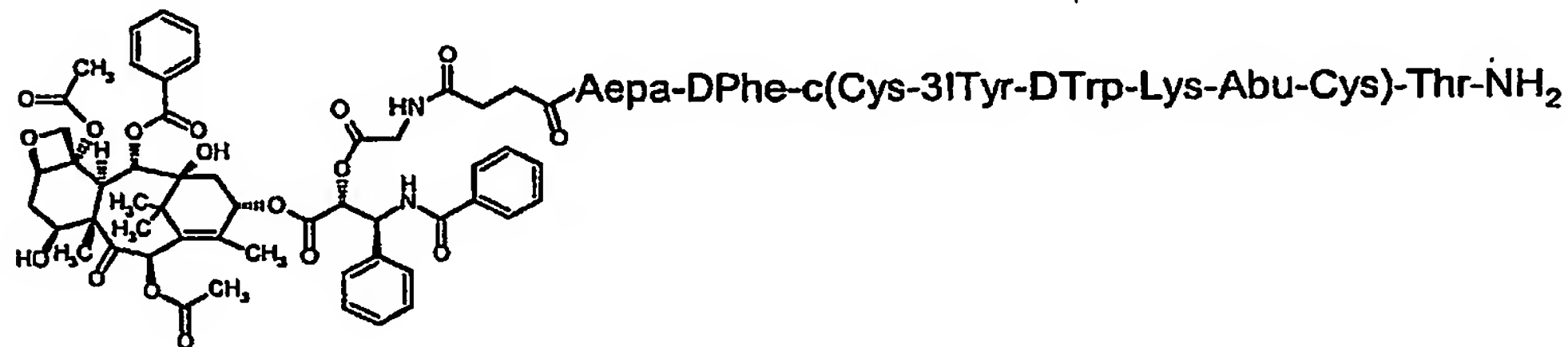
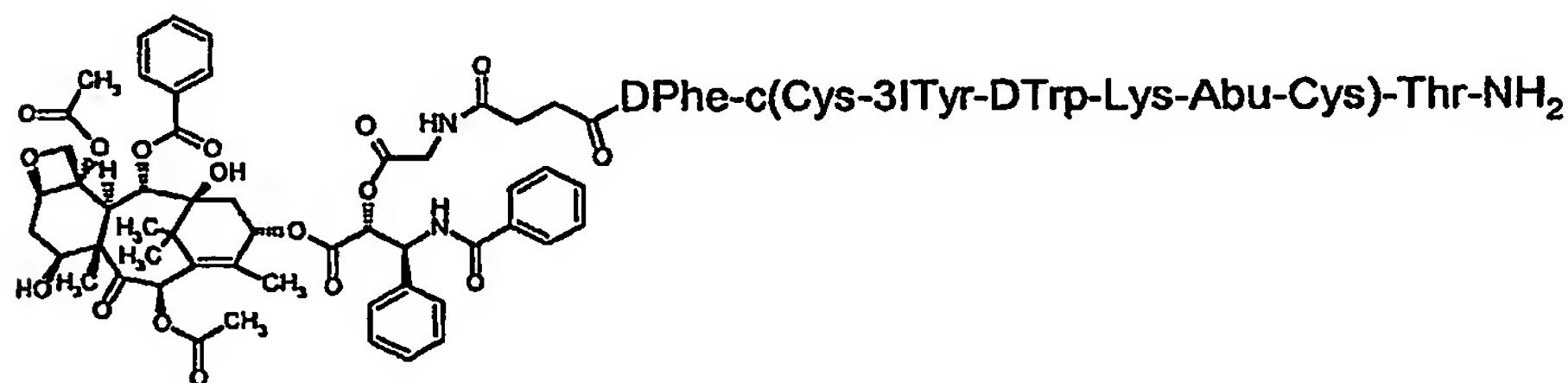
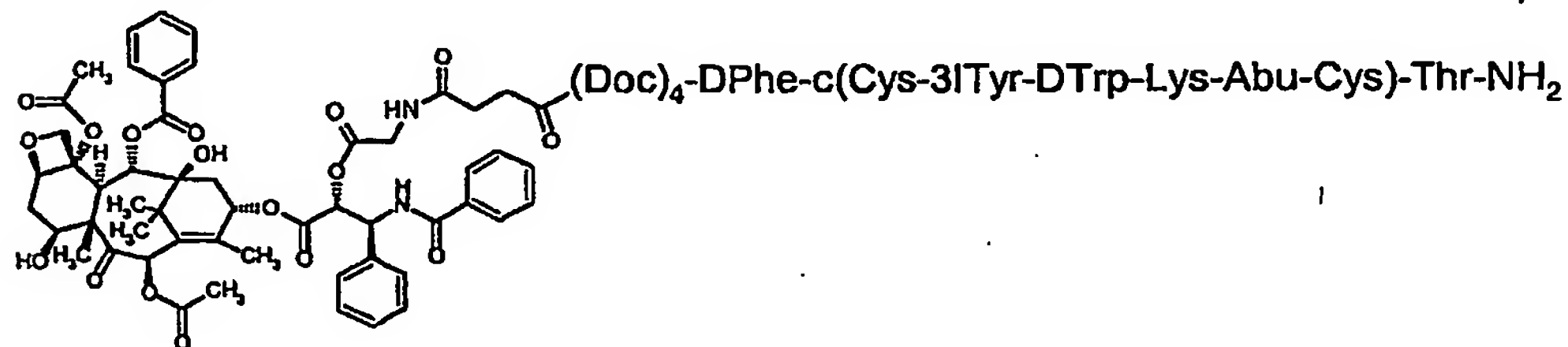
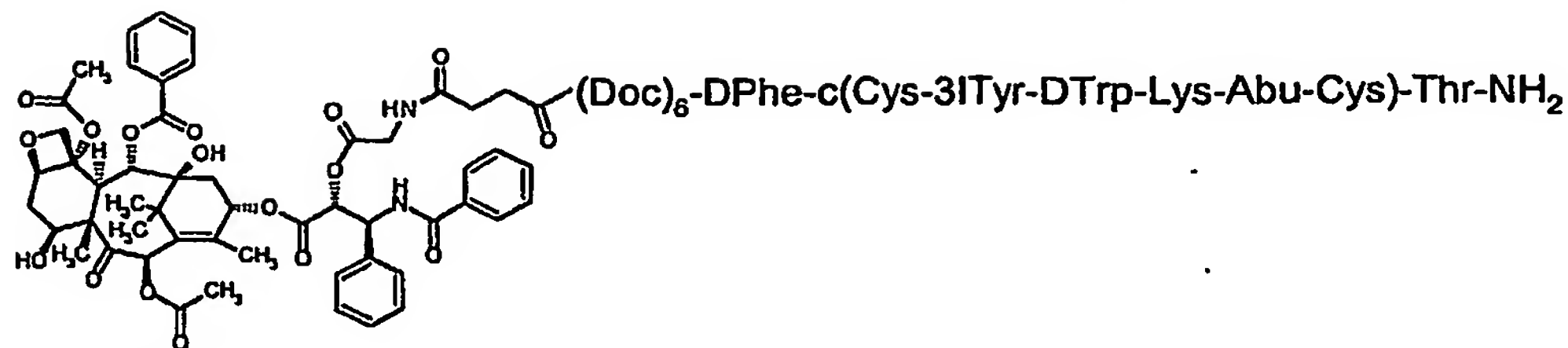
Appendix I

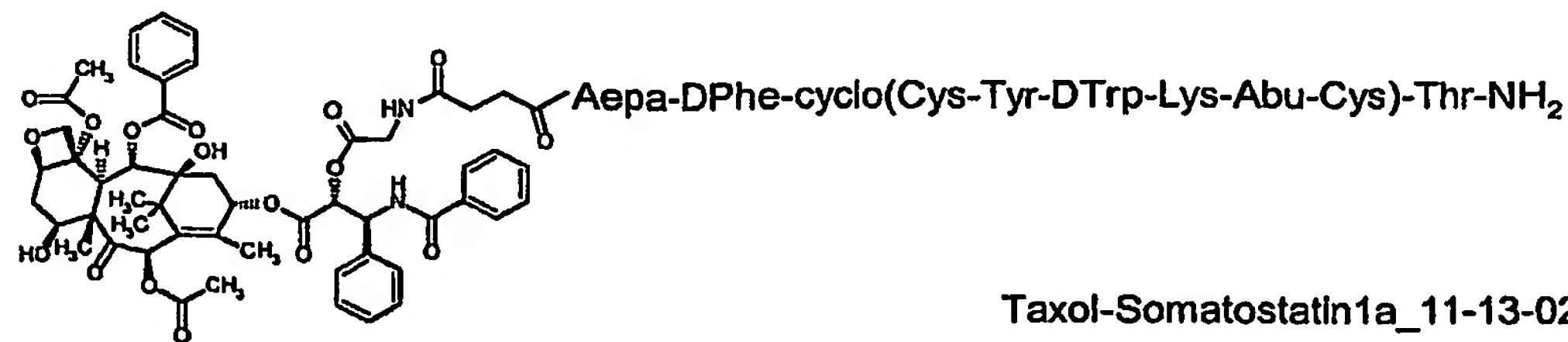
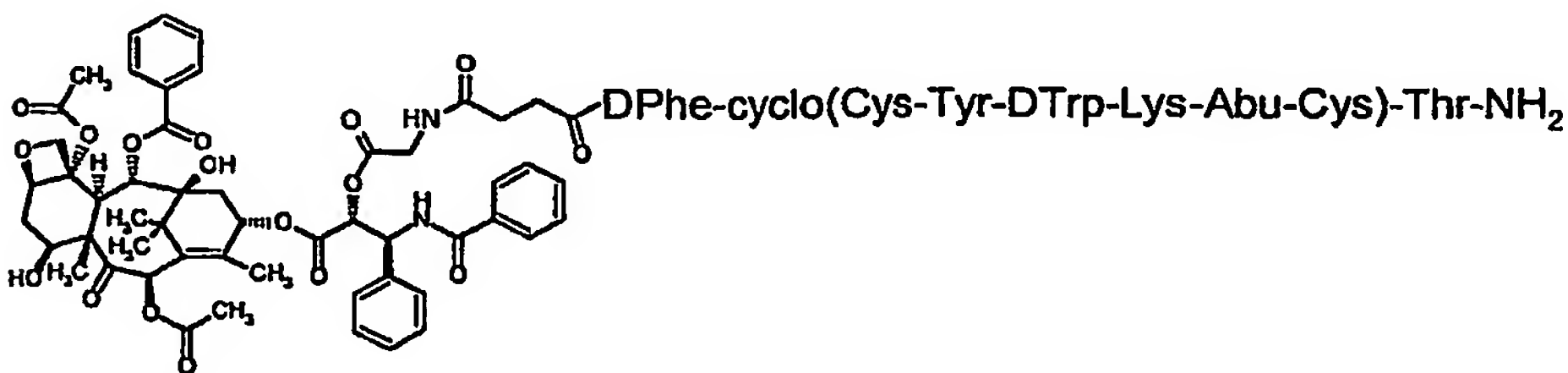
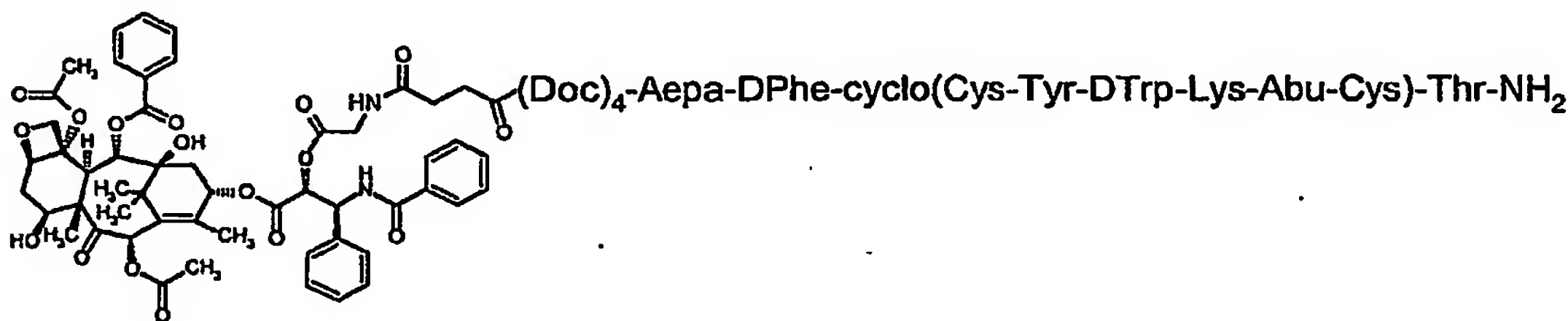
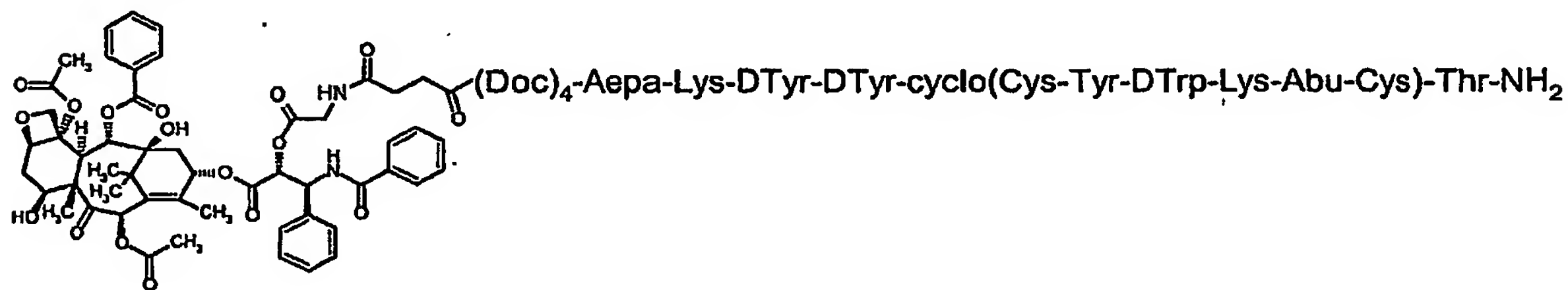
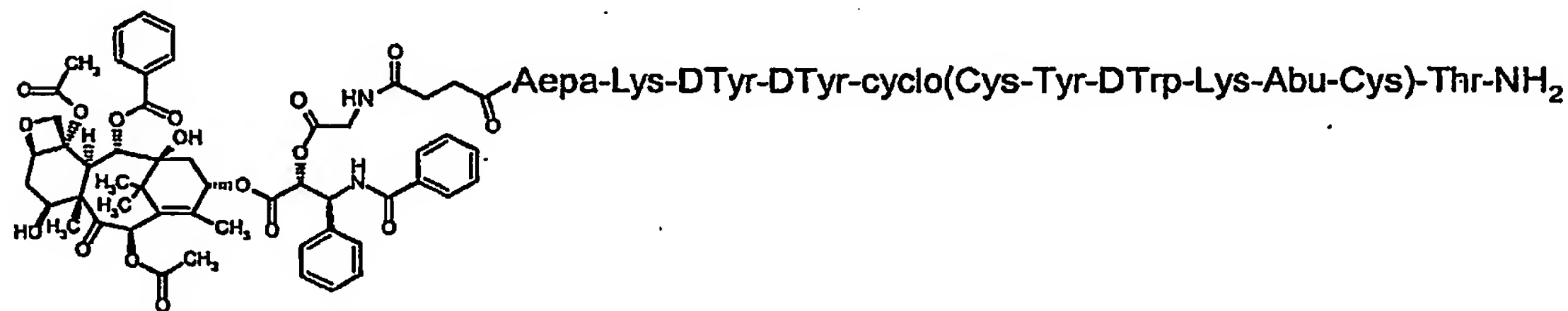
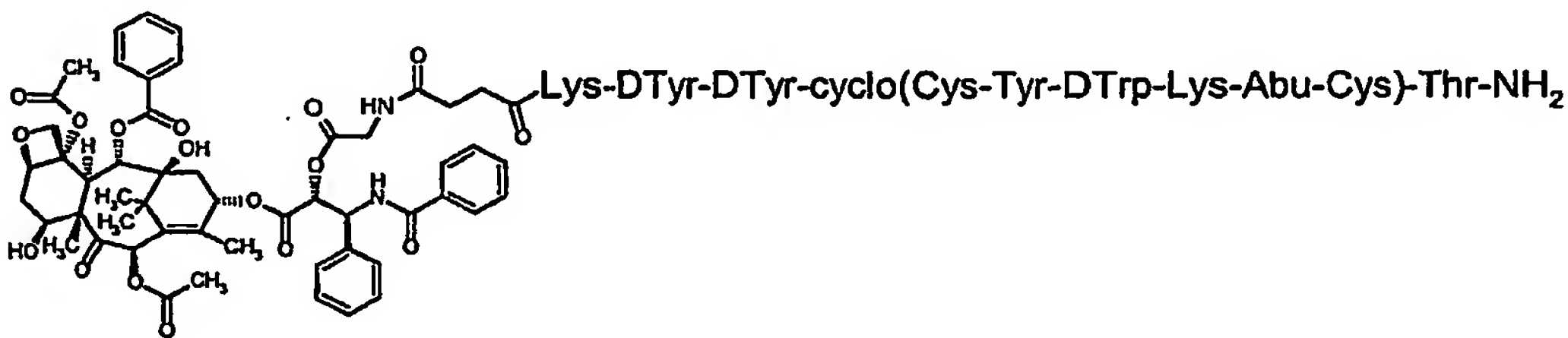
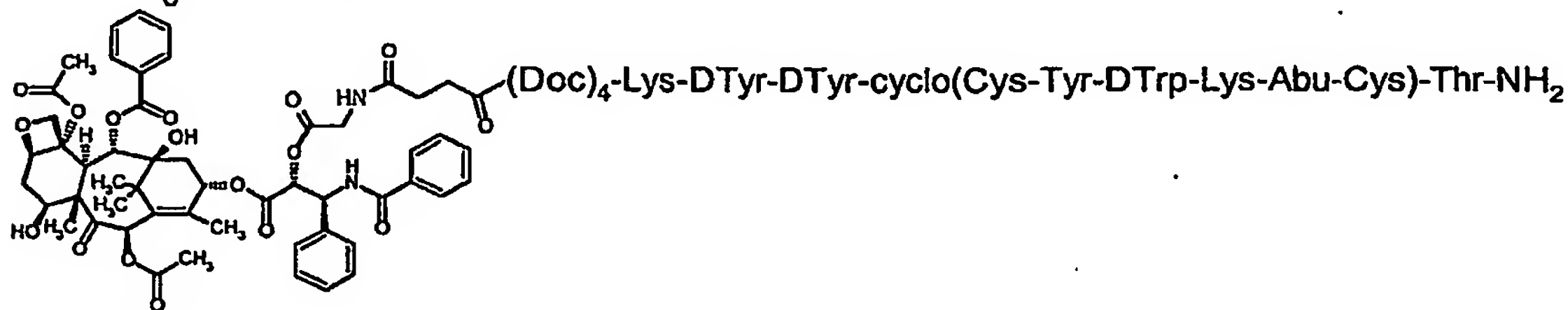
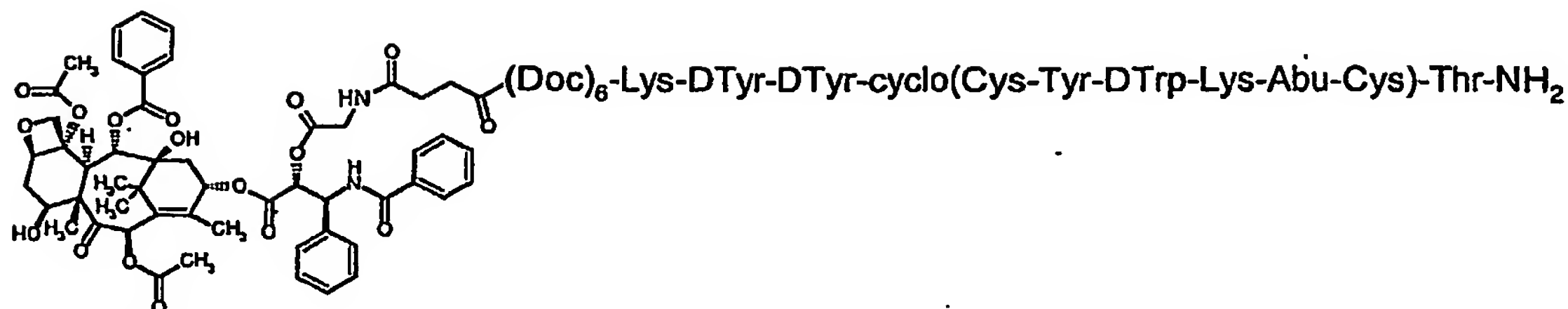
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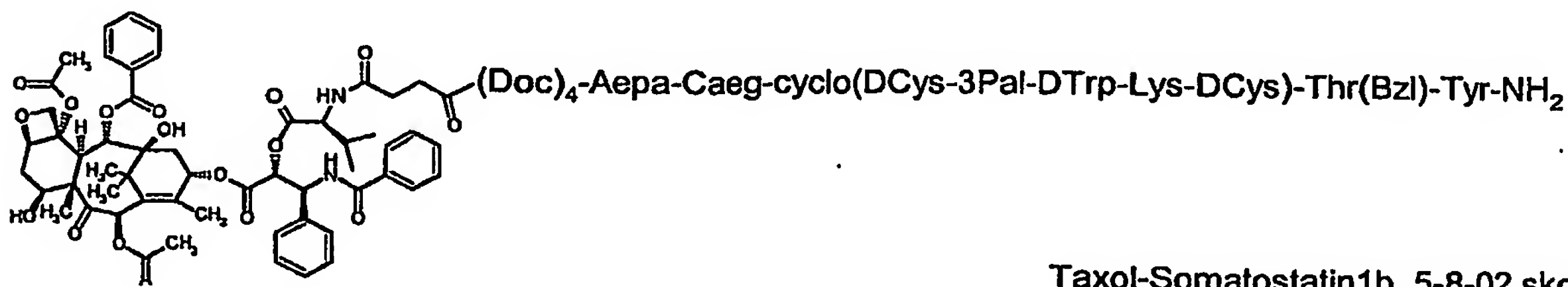
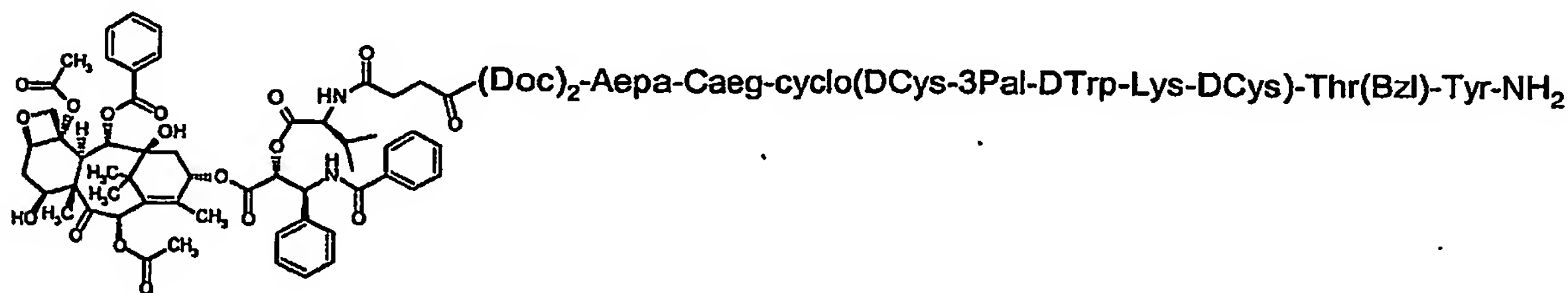
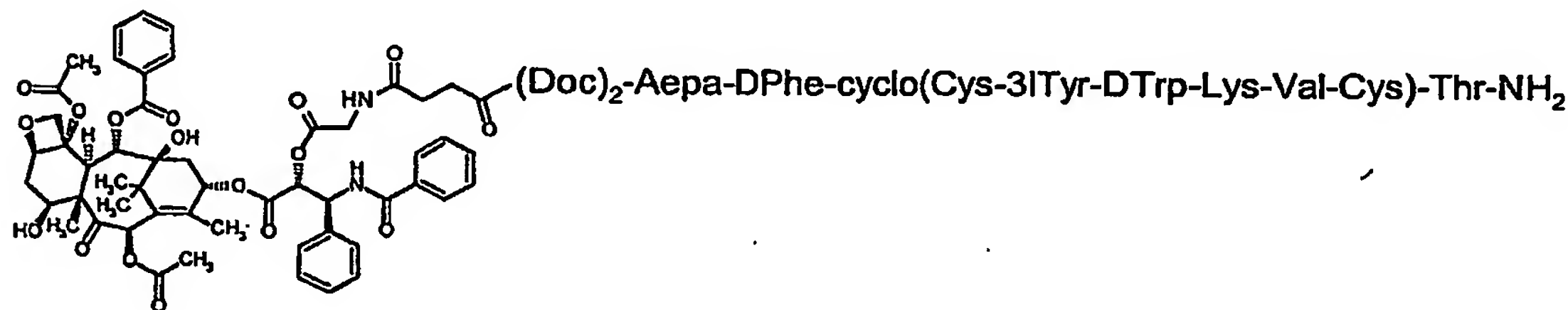
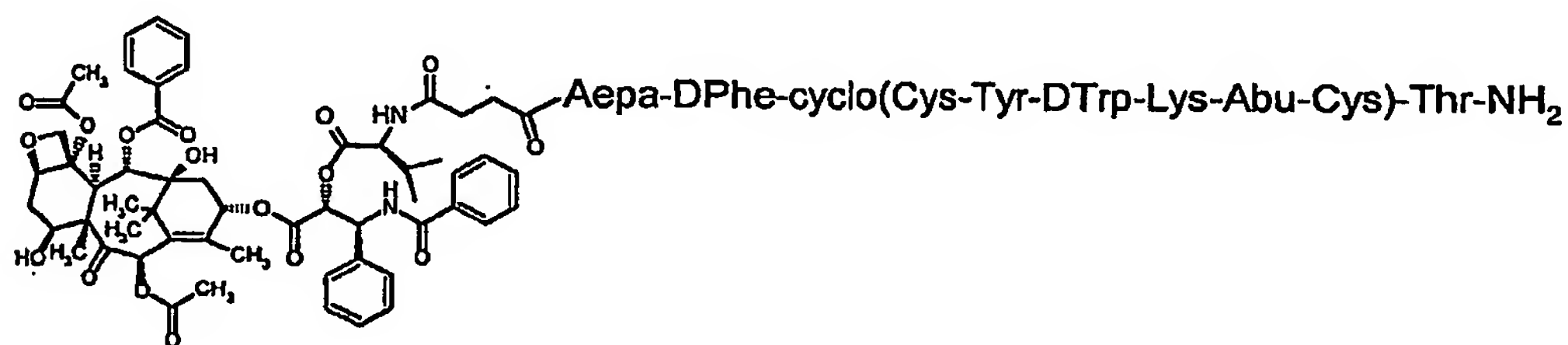
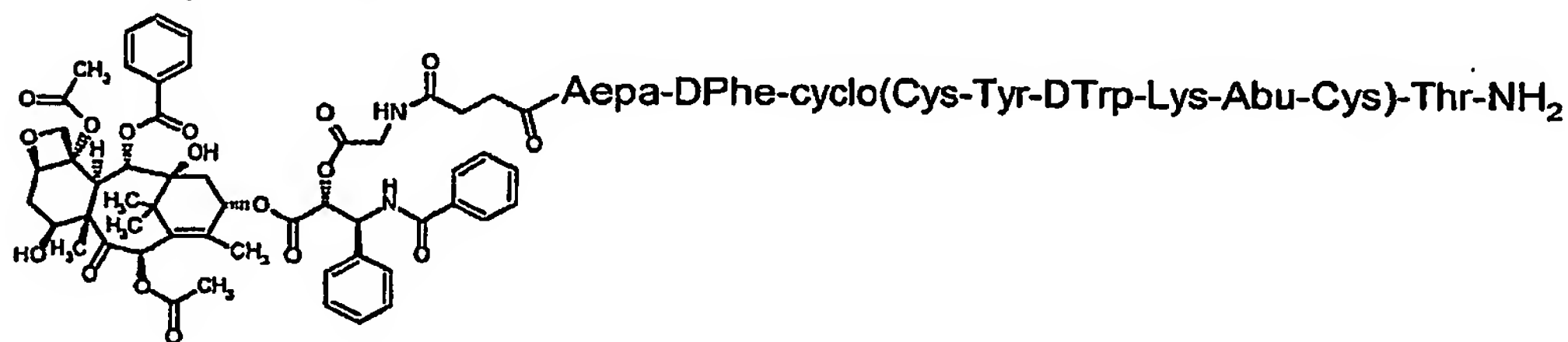
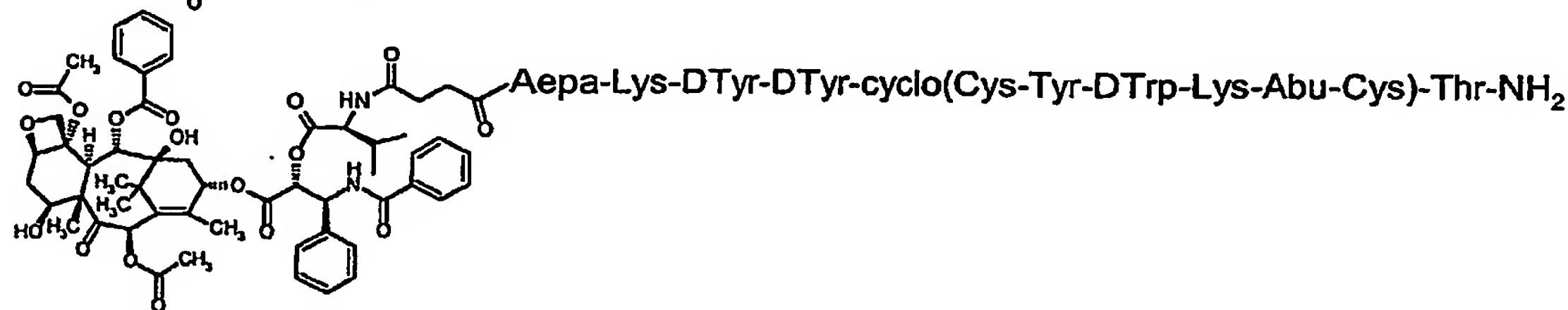
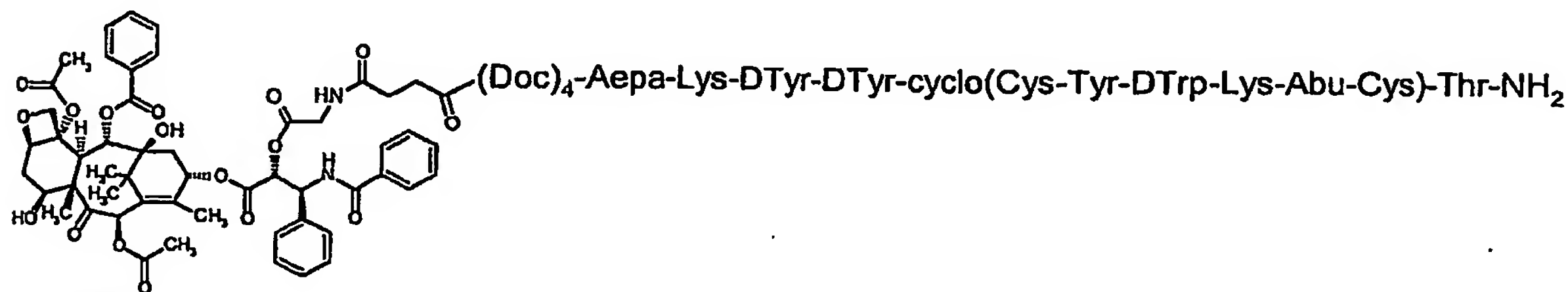
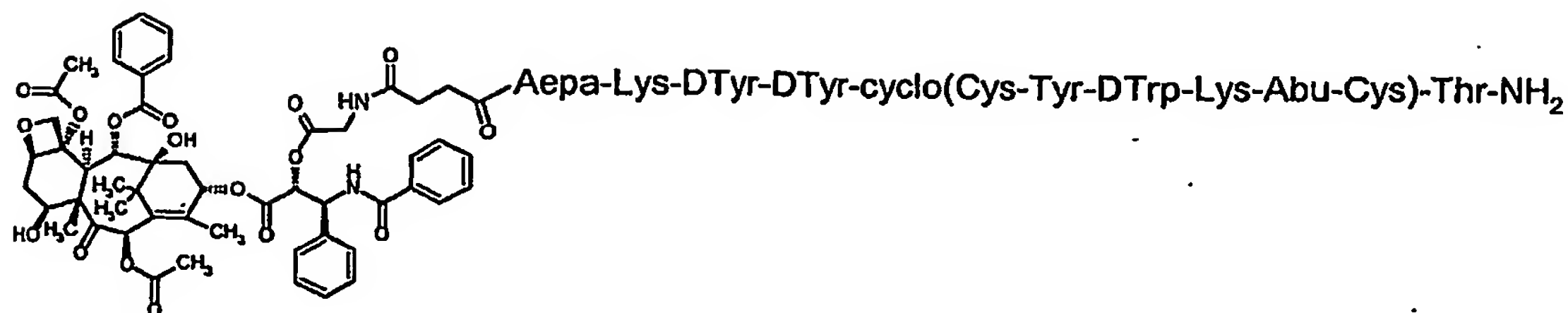


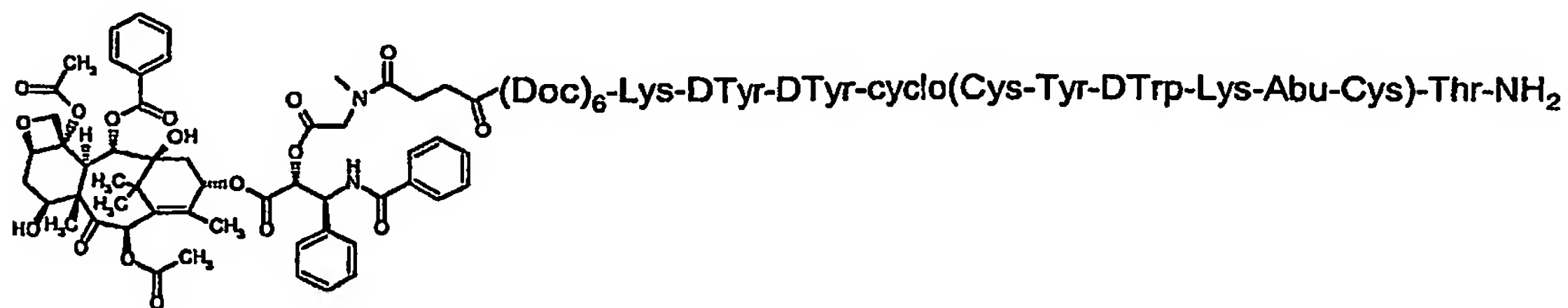
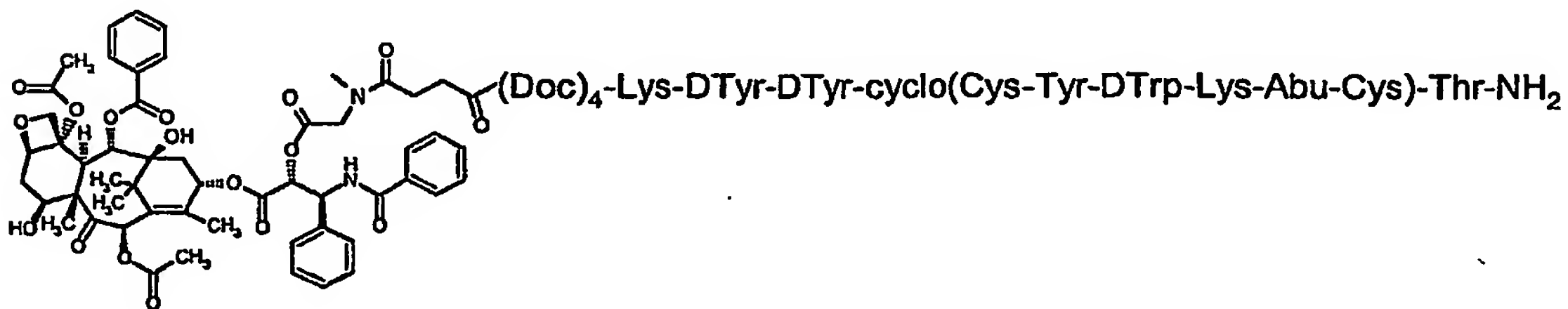
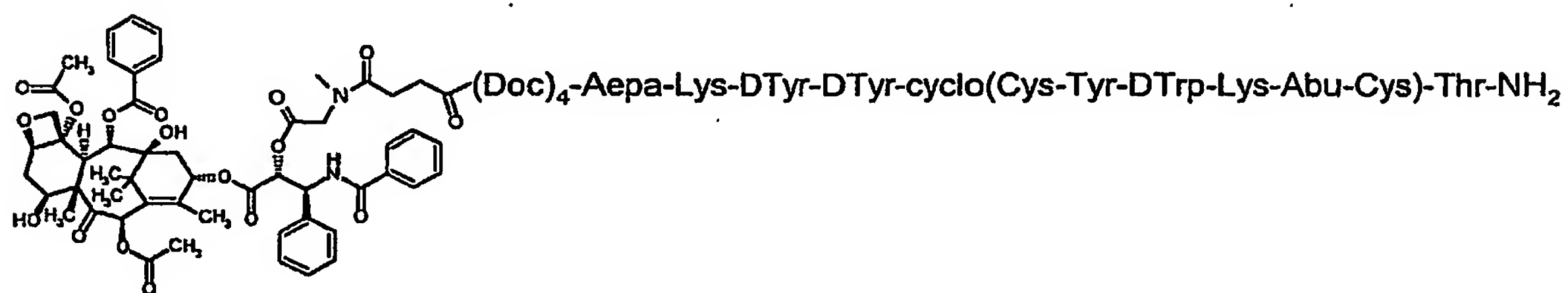
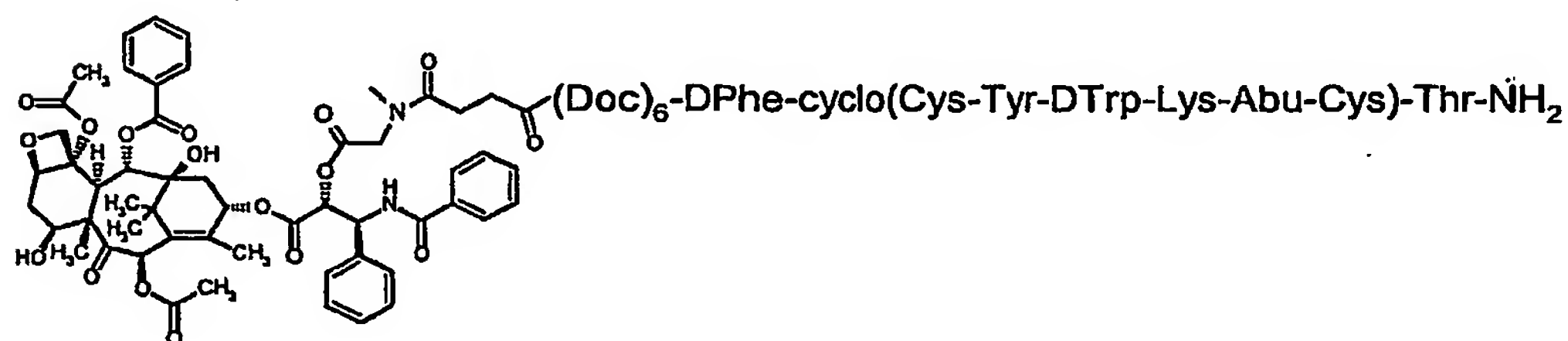
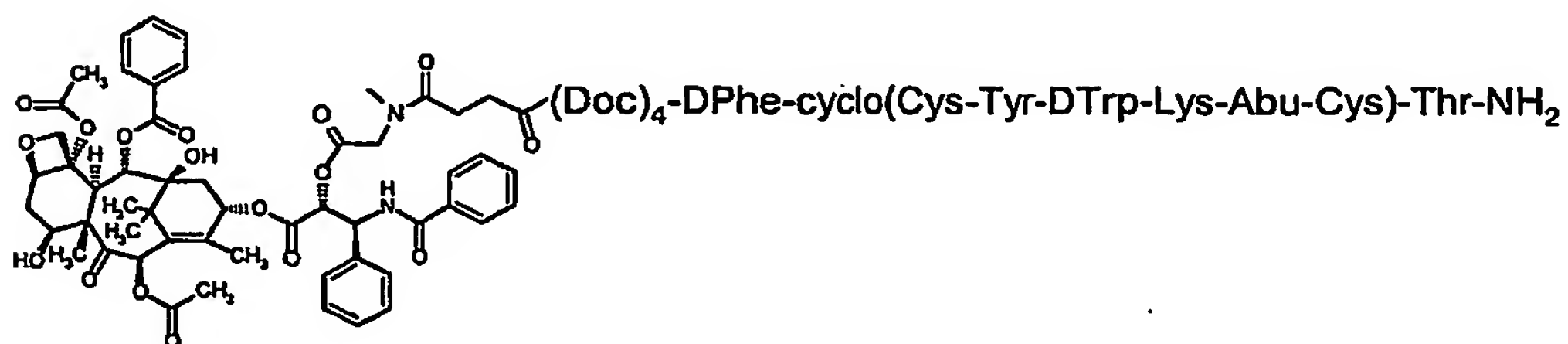
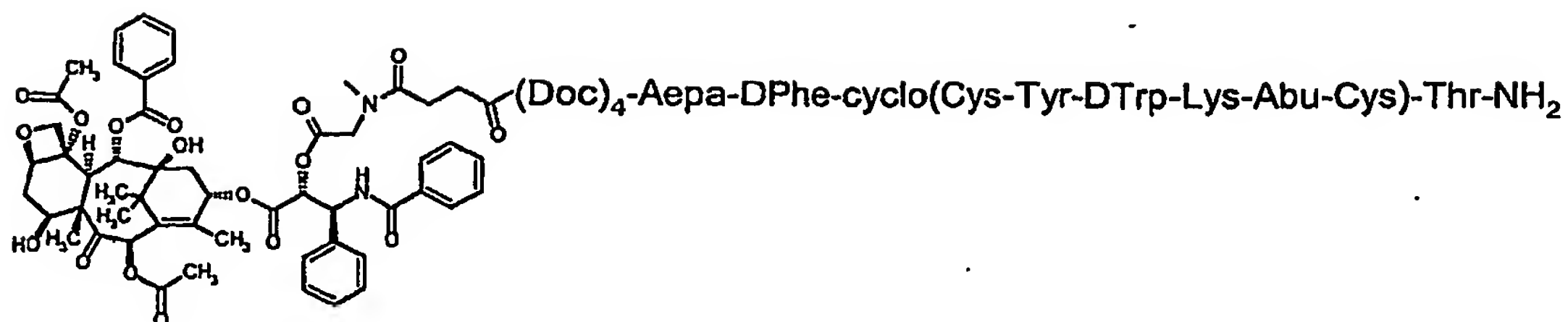


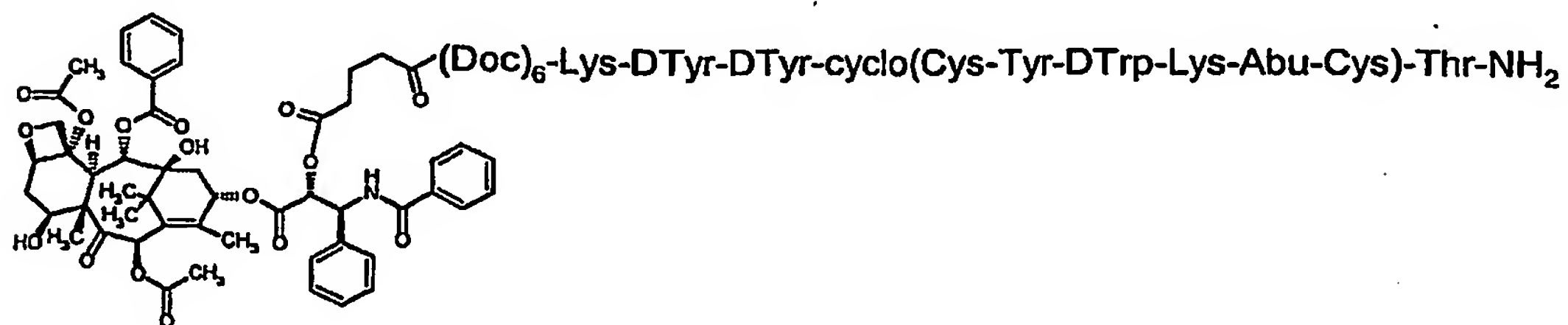
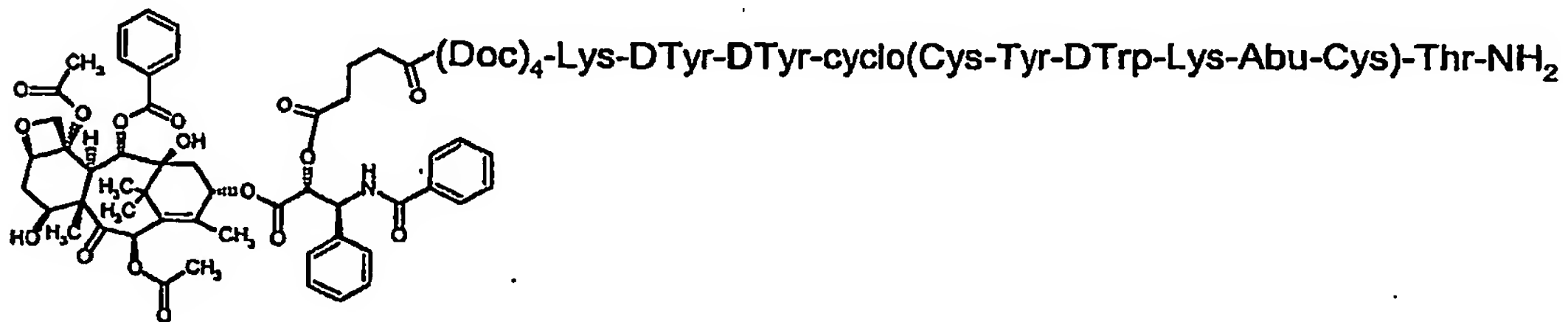
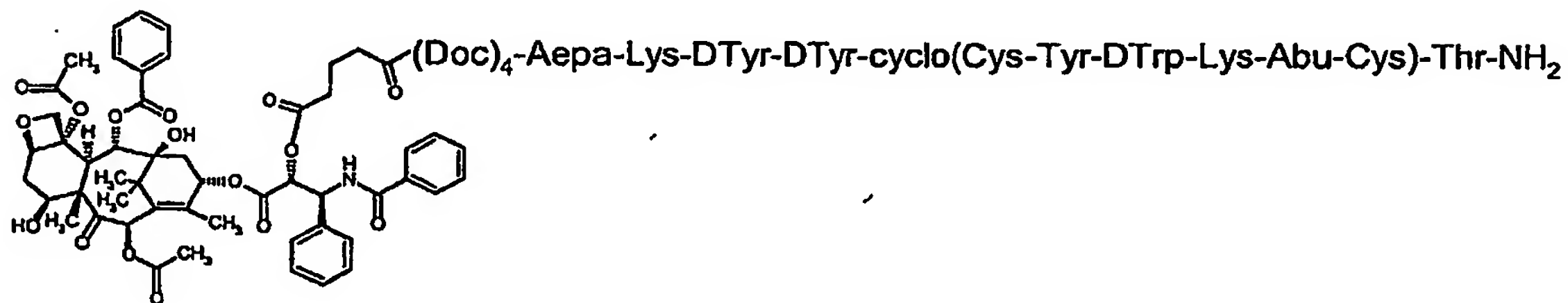
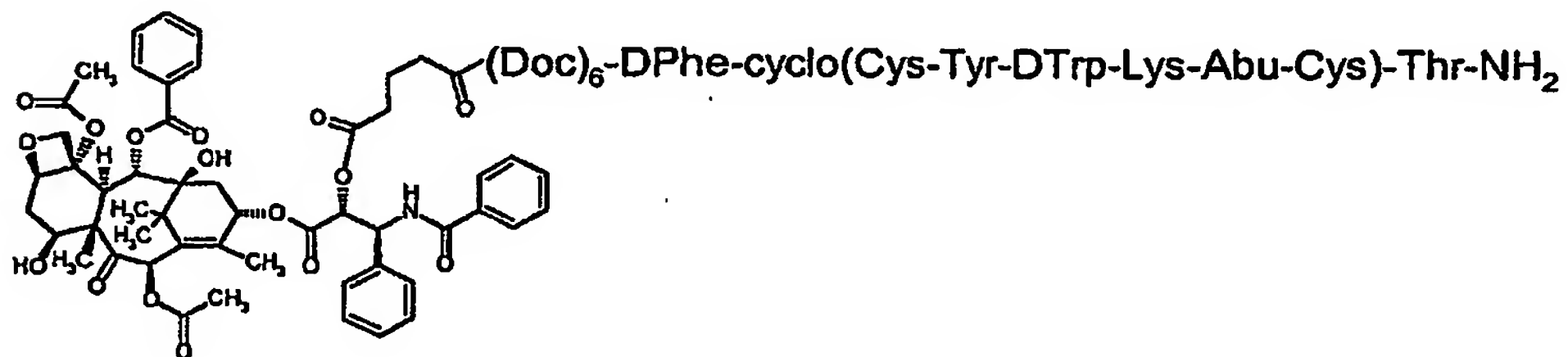
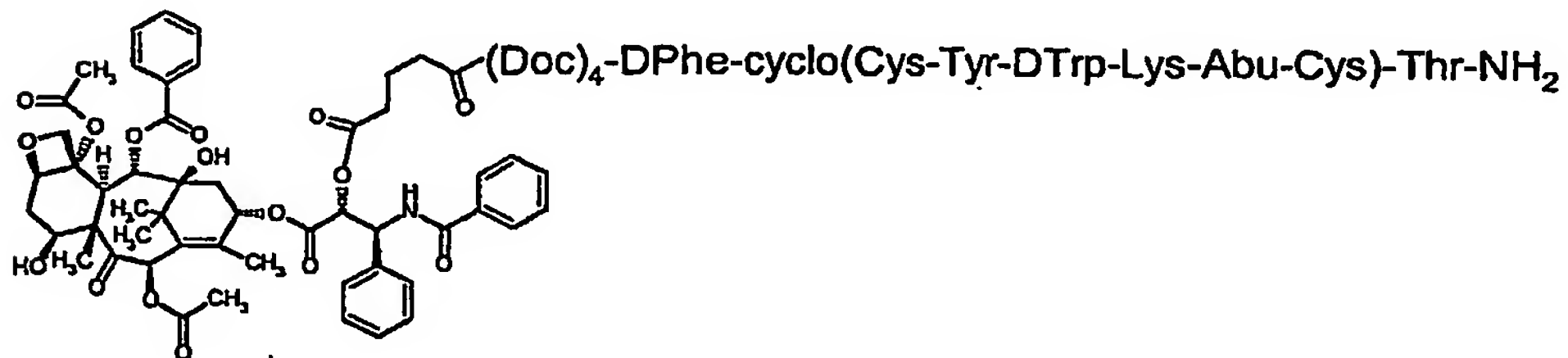
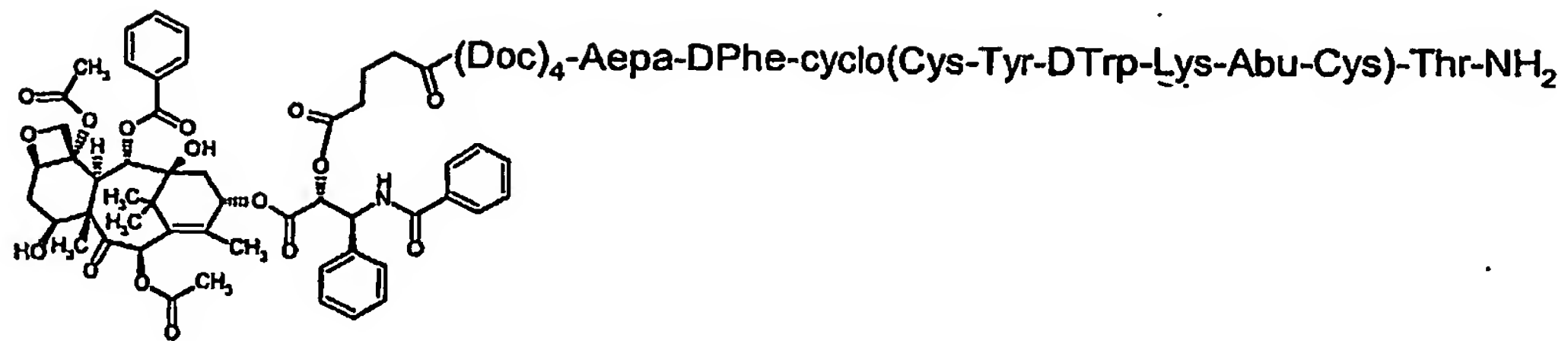


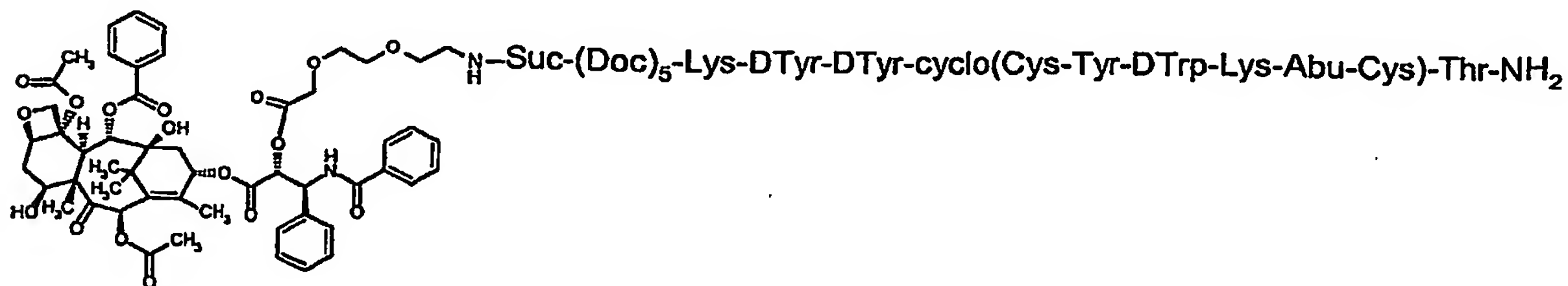
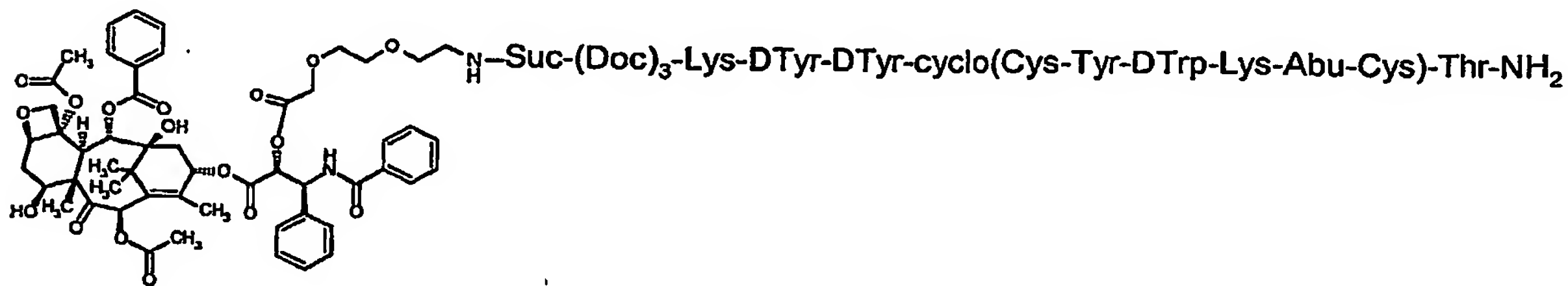
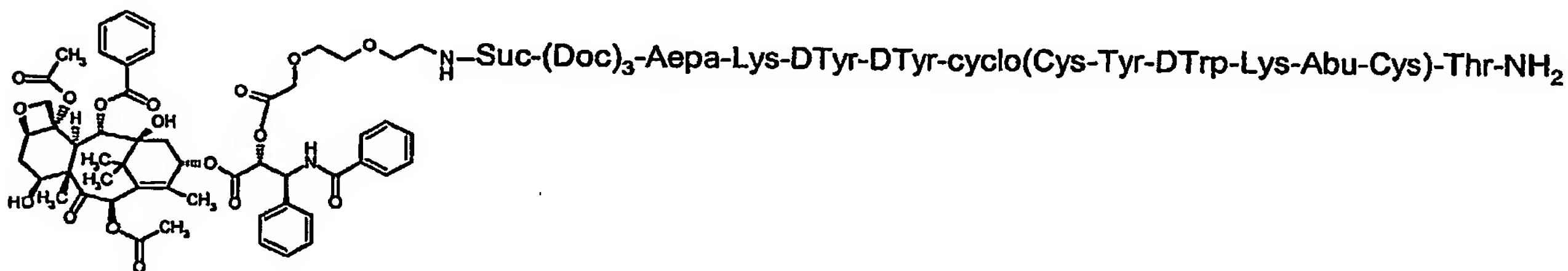
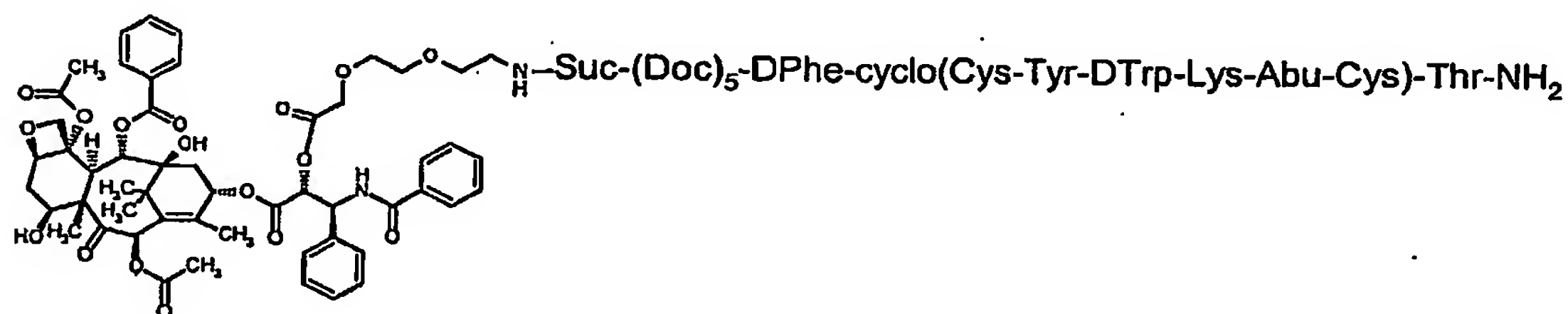
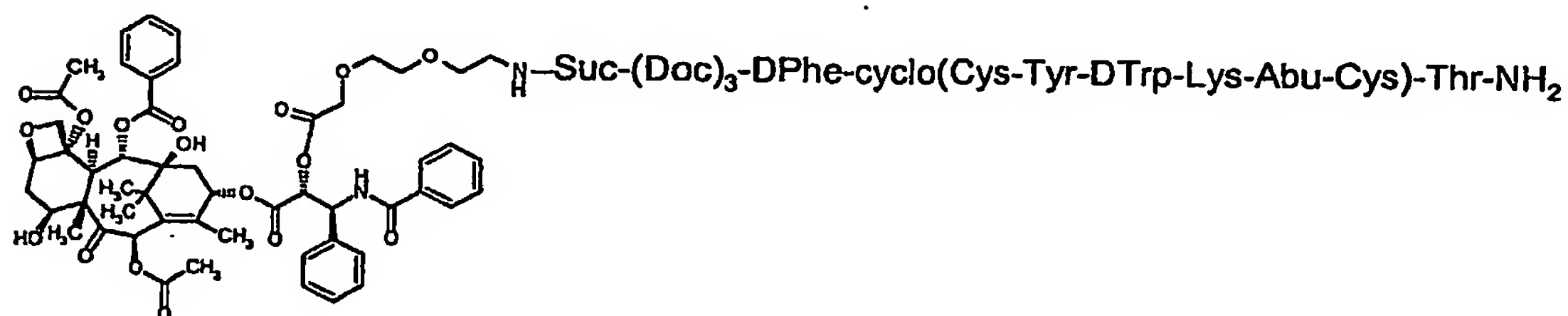


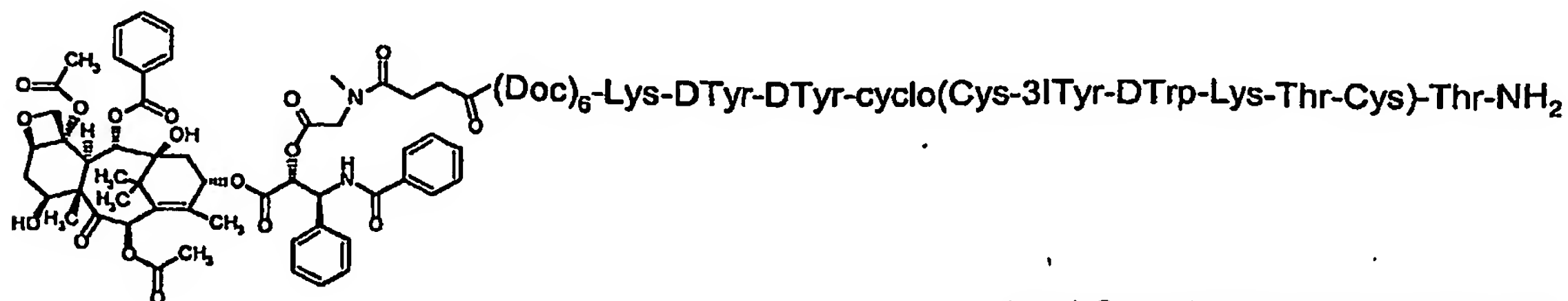
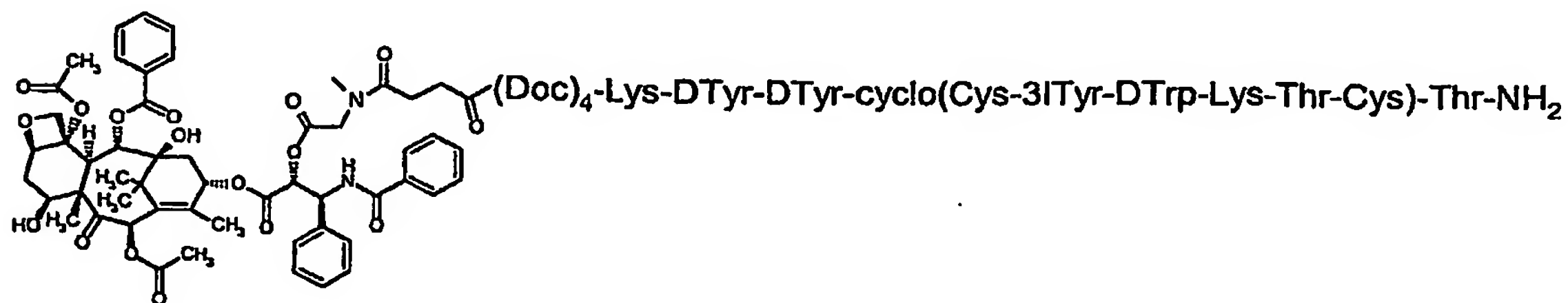
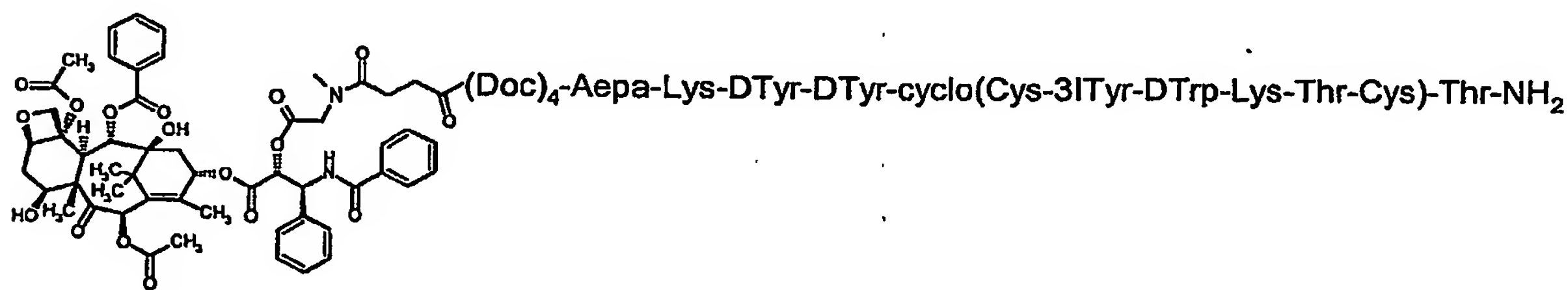
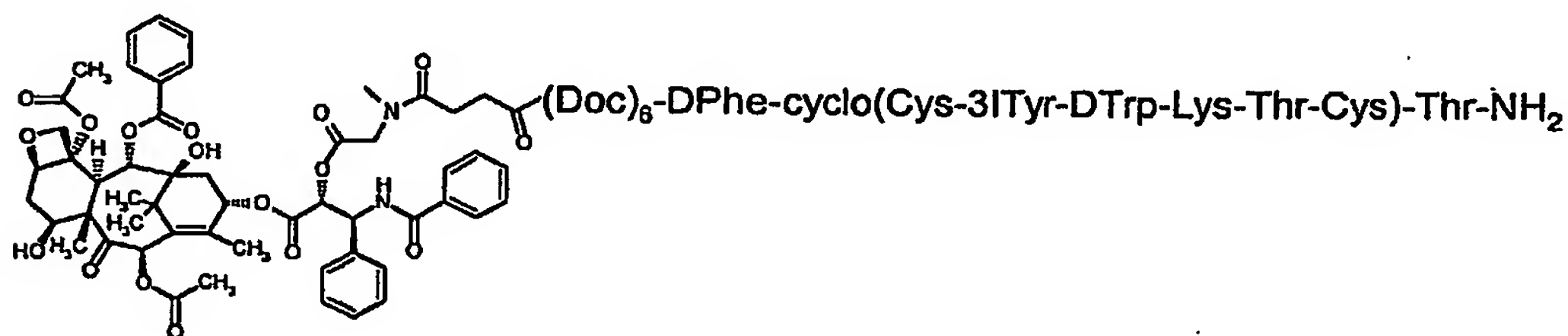
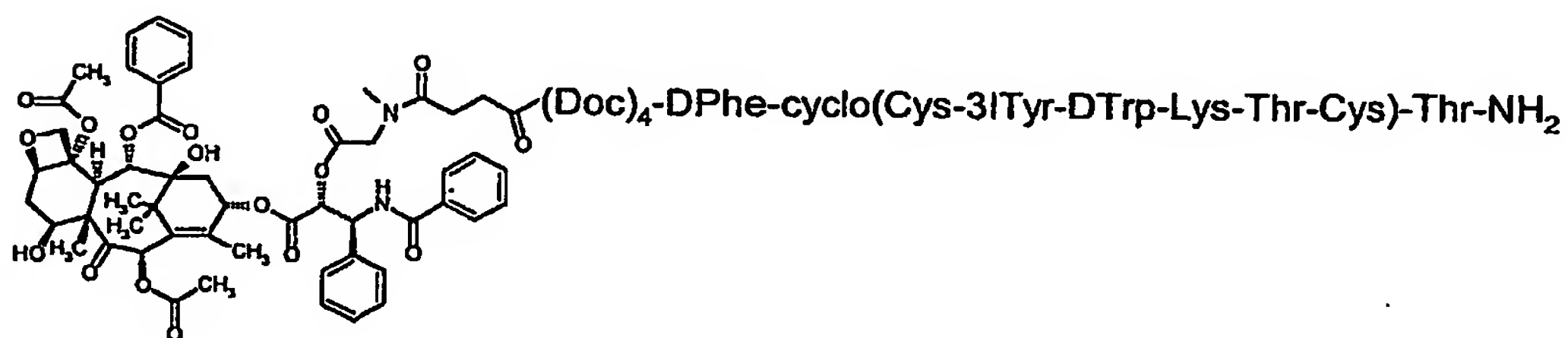
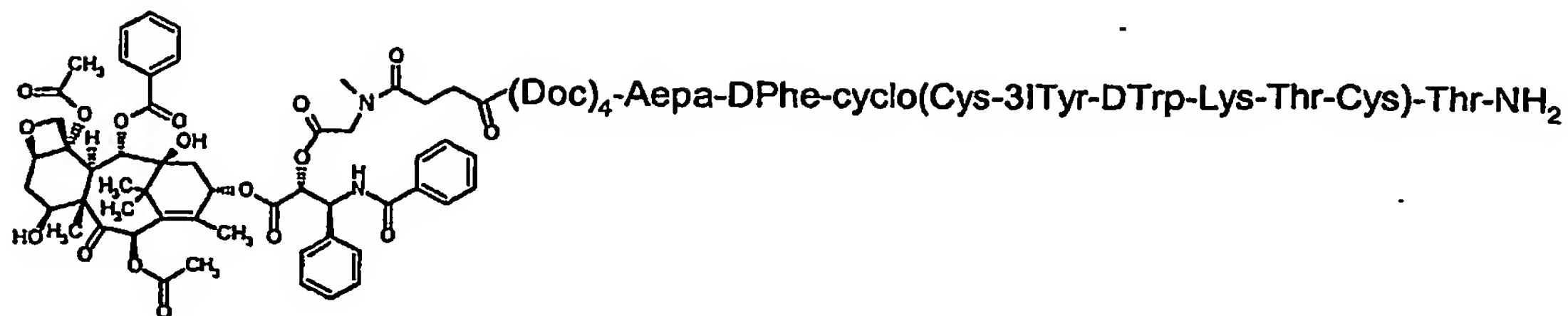


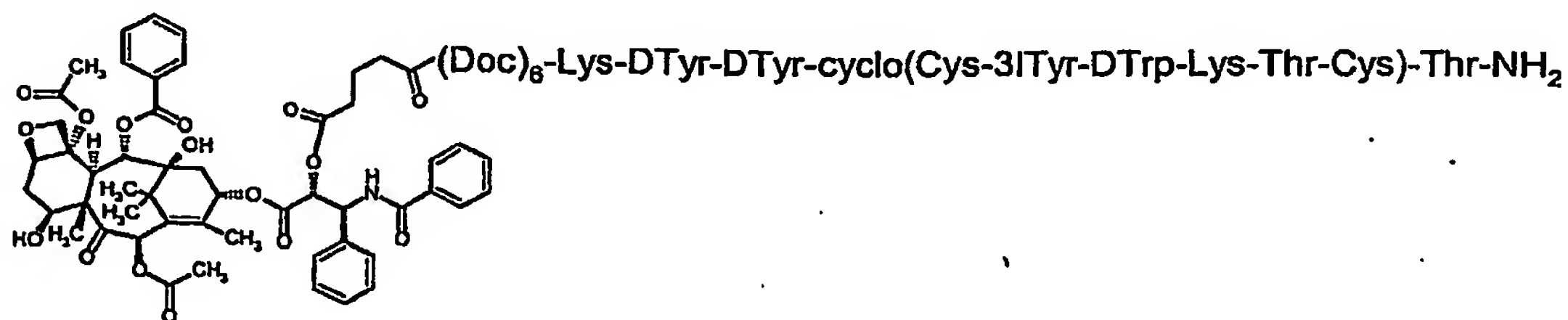
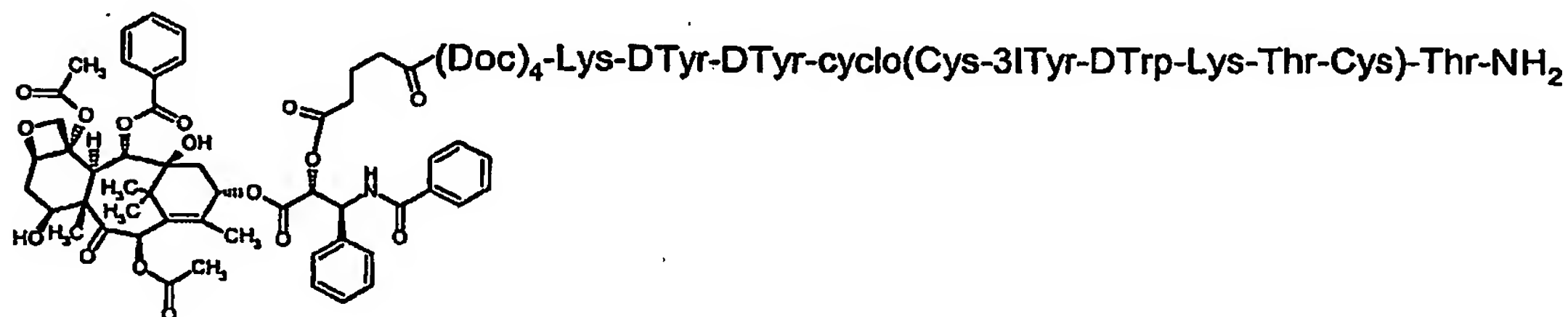
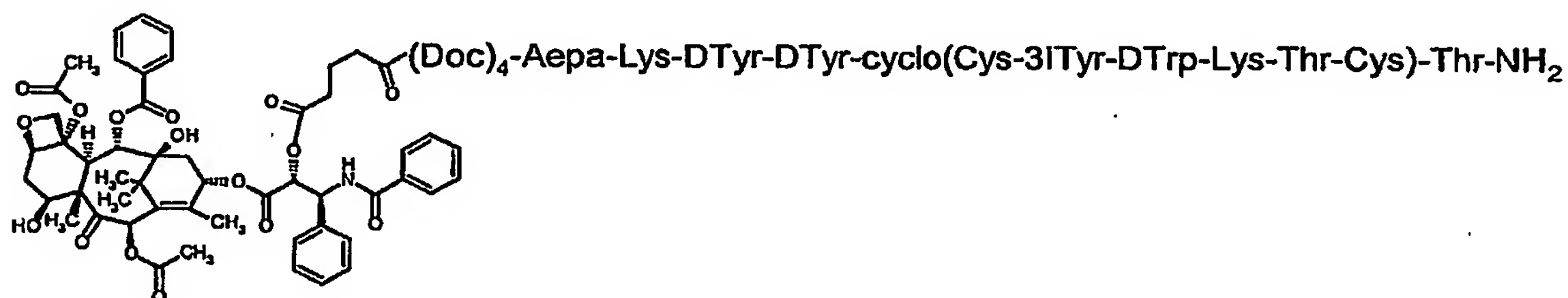
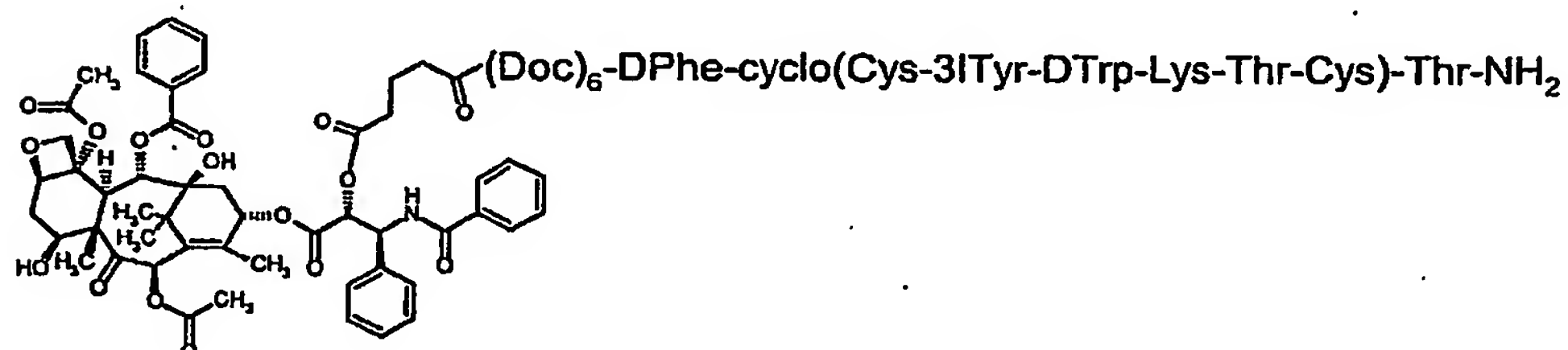
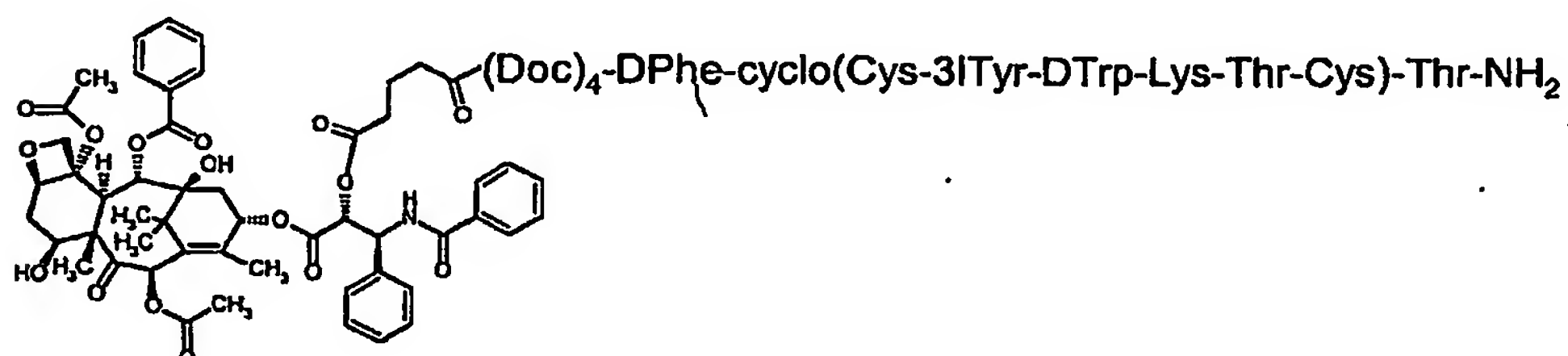
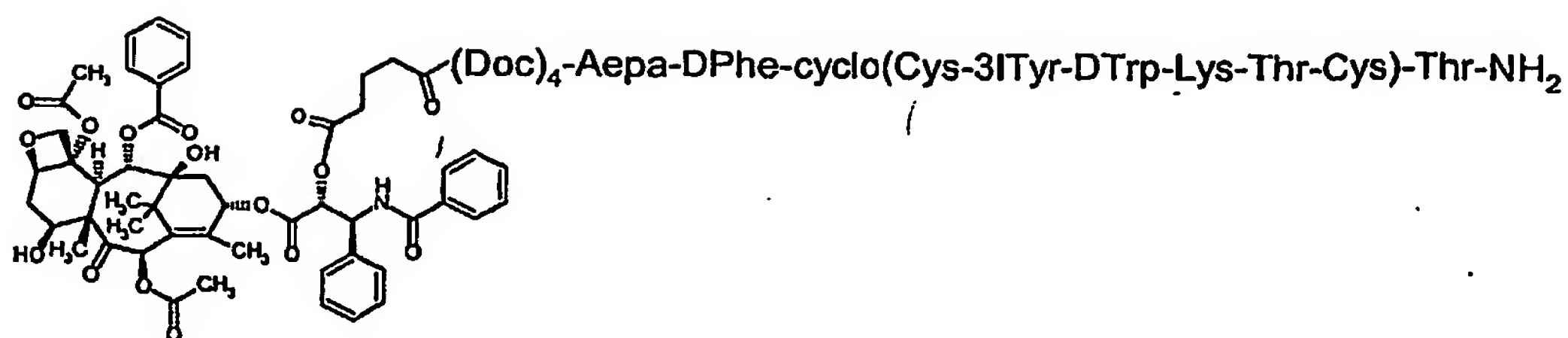


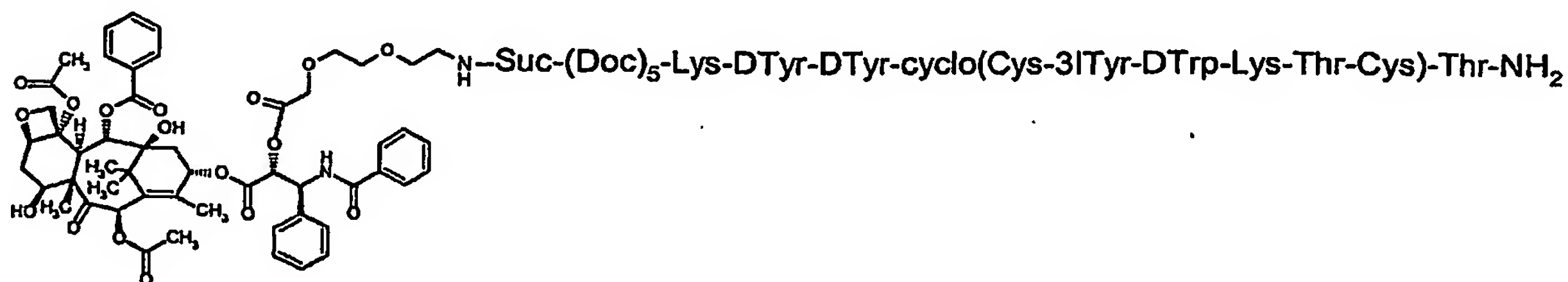
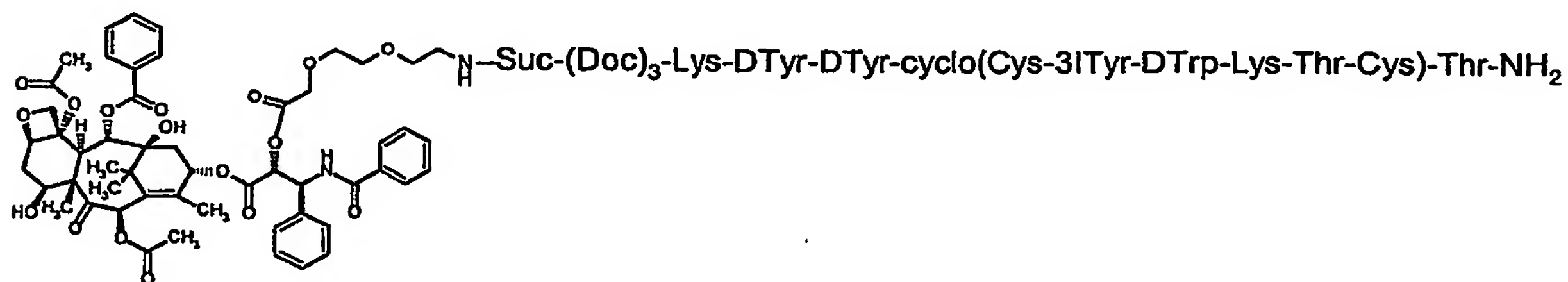
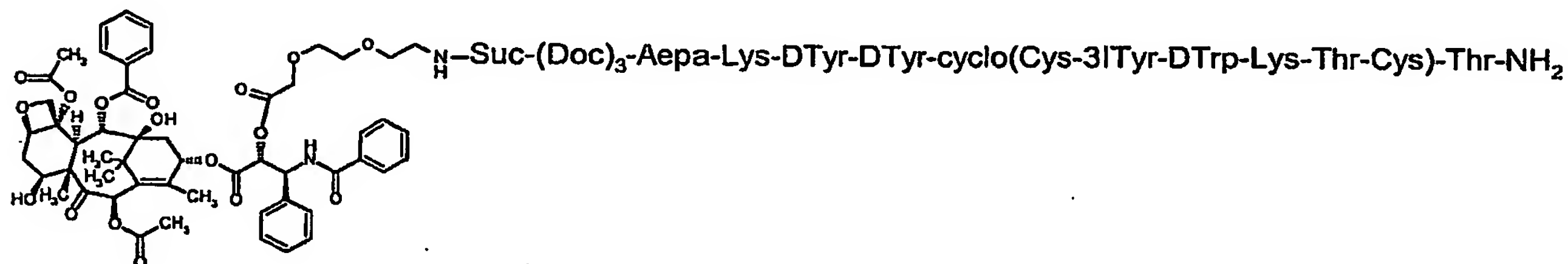
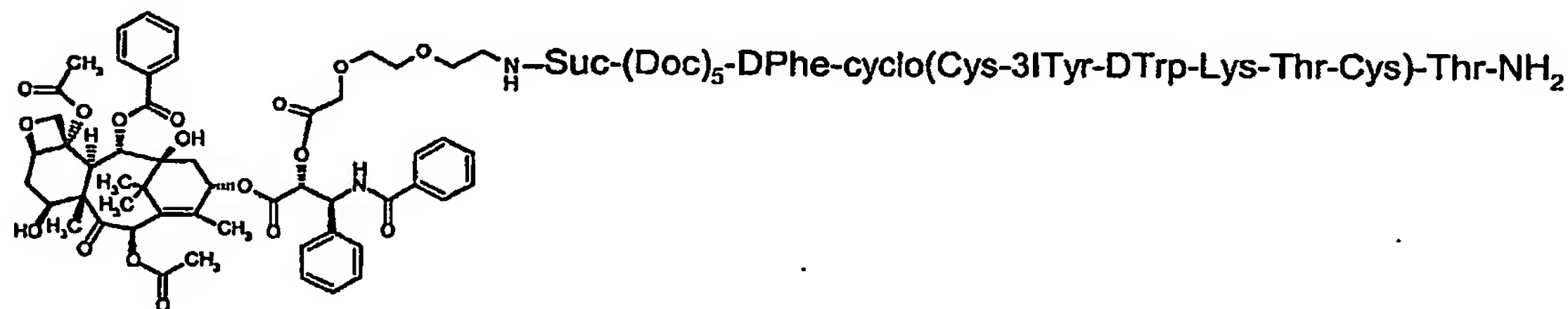
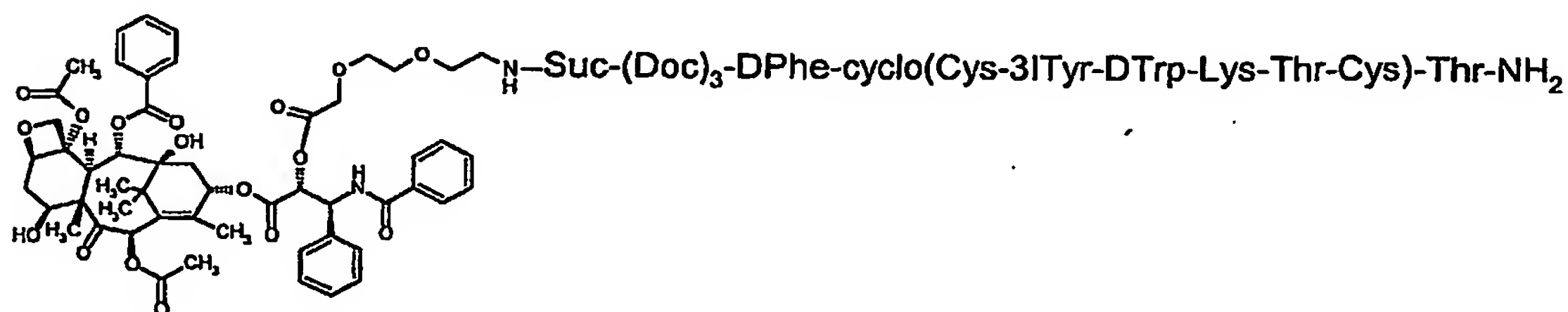
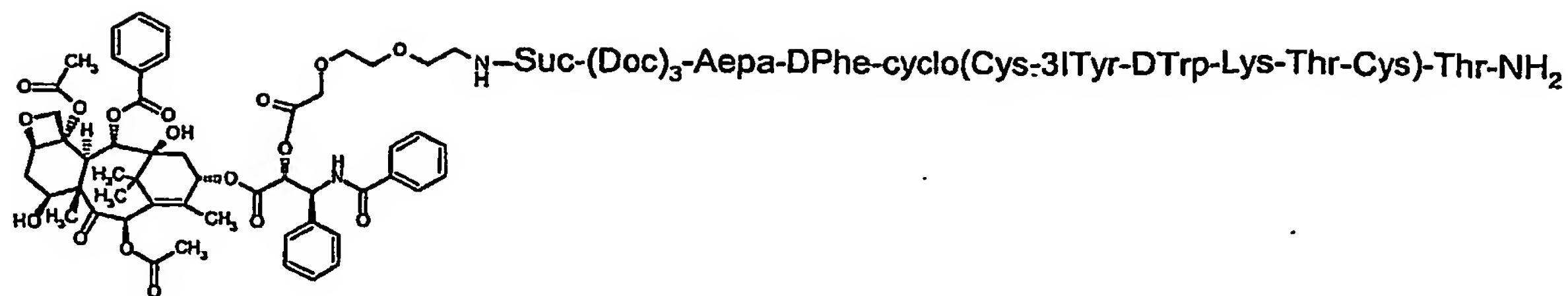


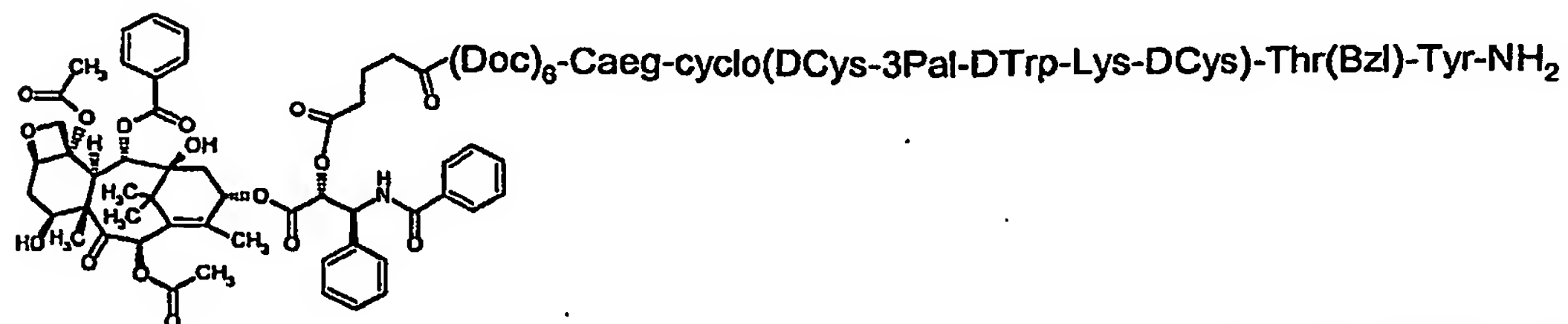
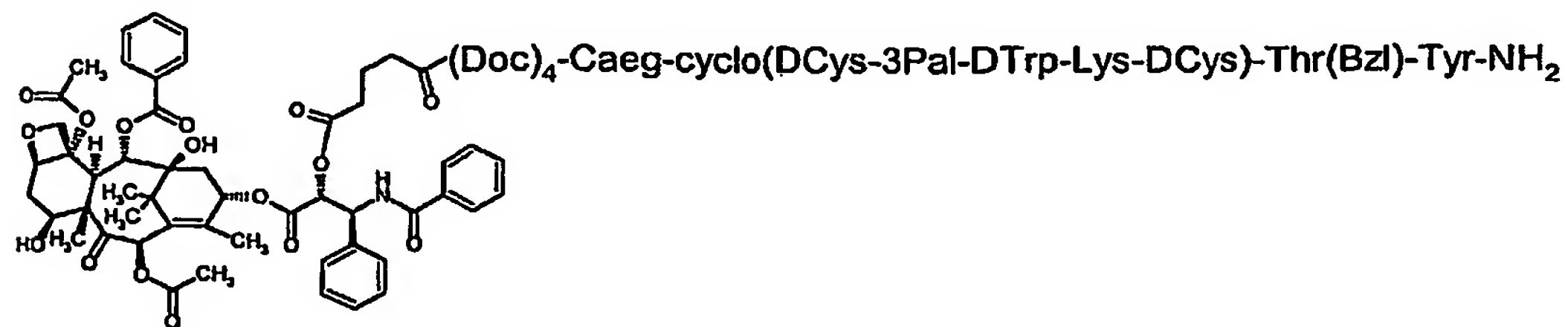
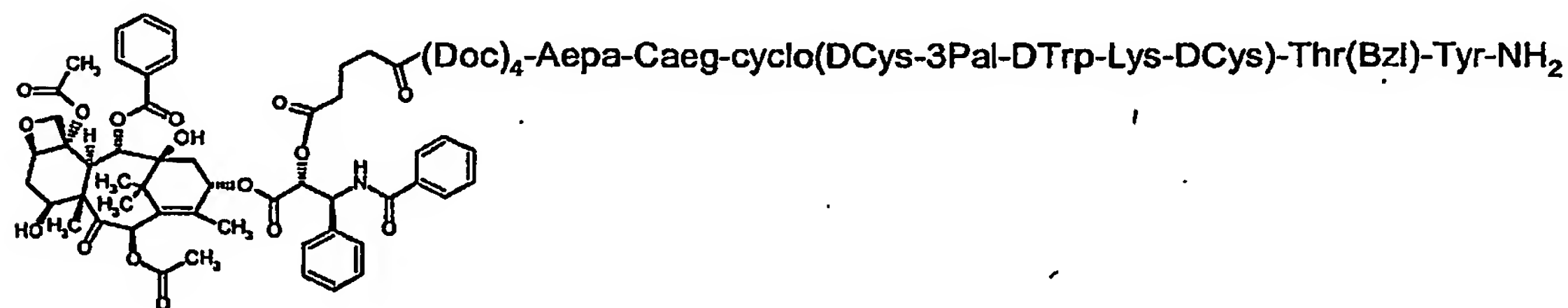
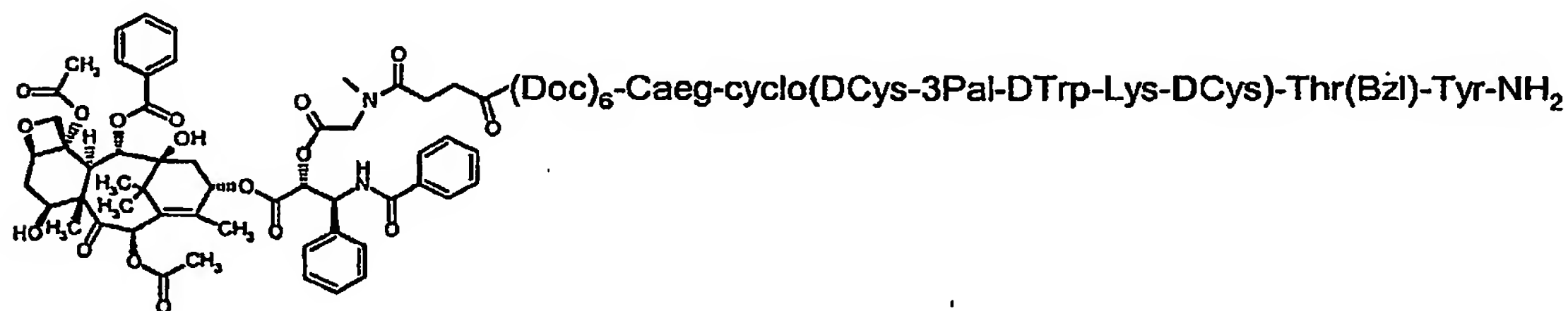
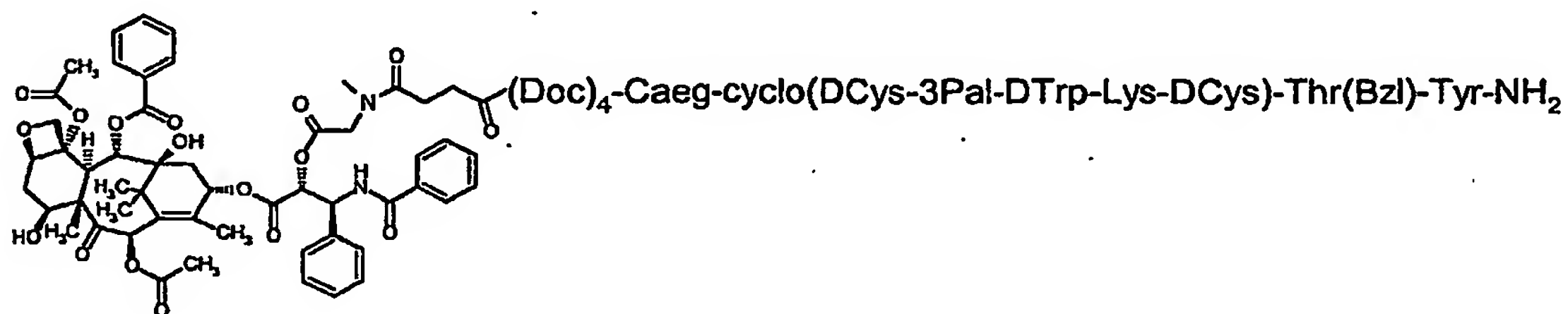
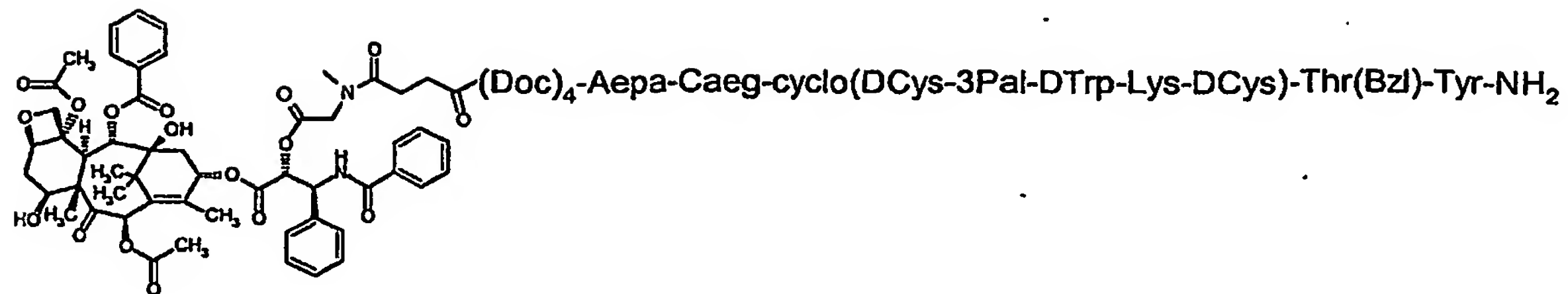


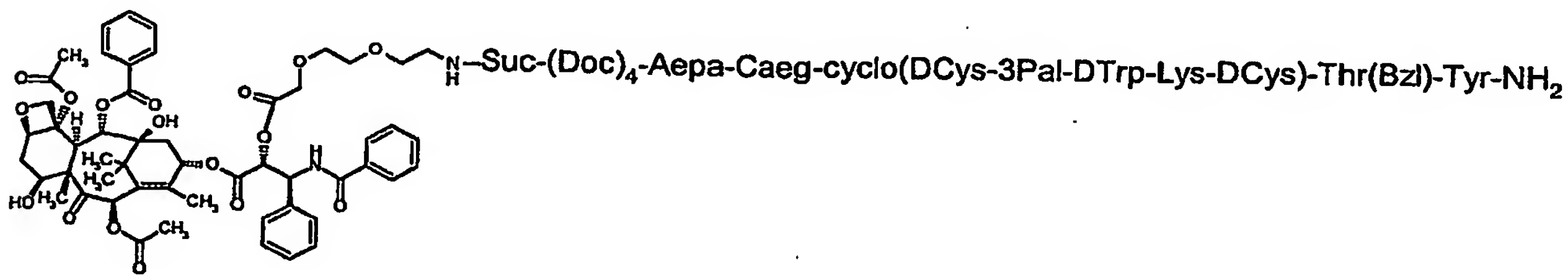
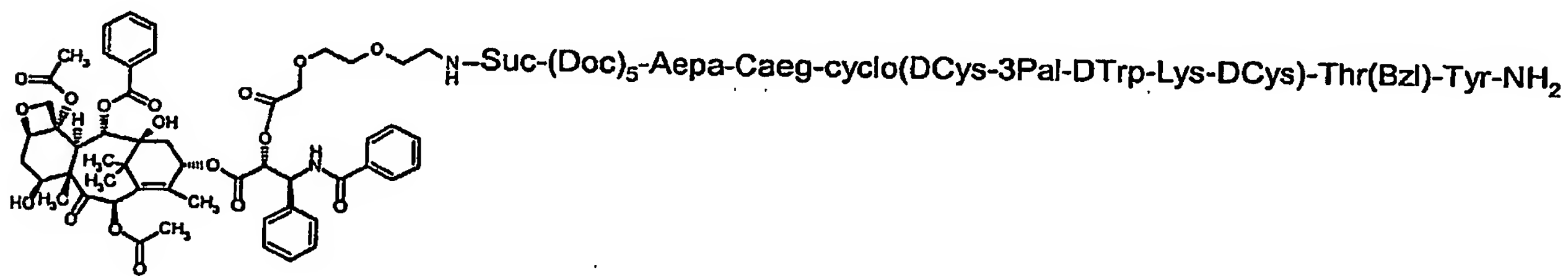
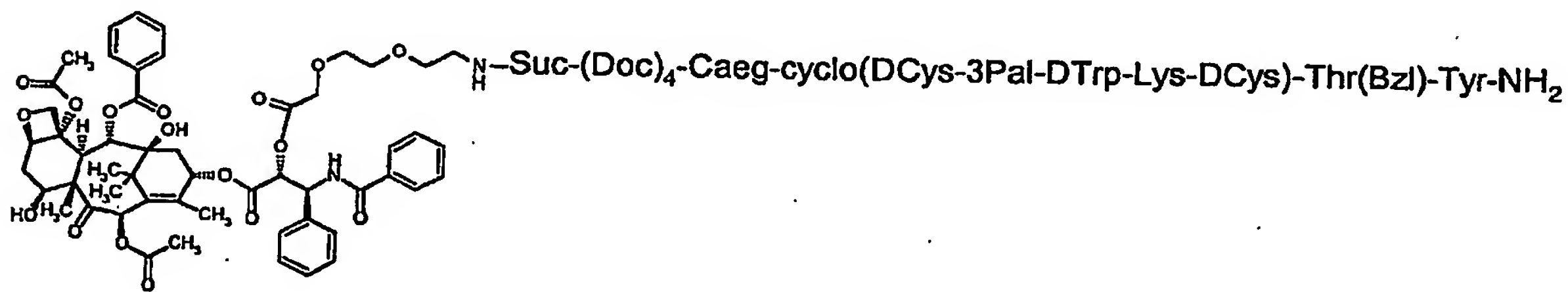
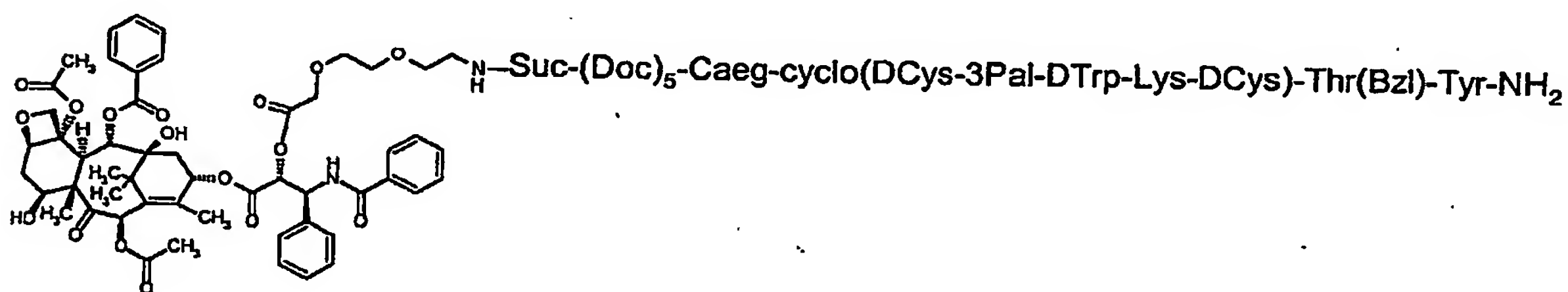
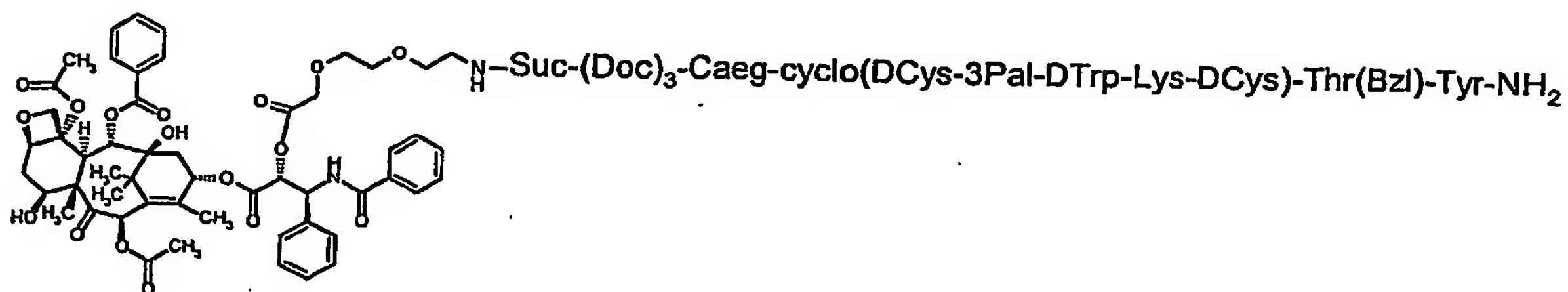
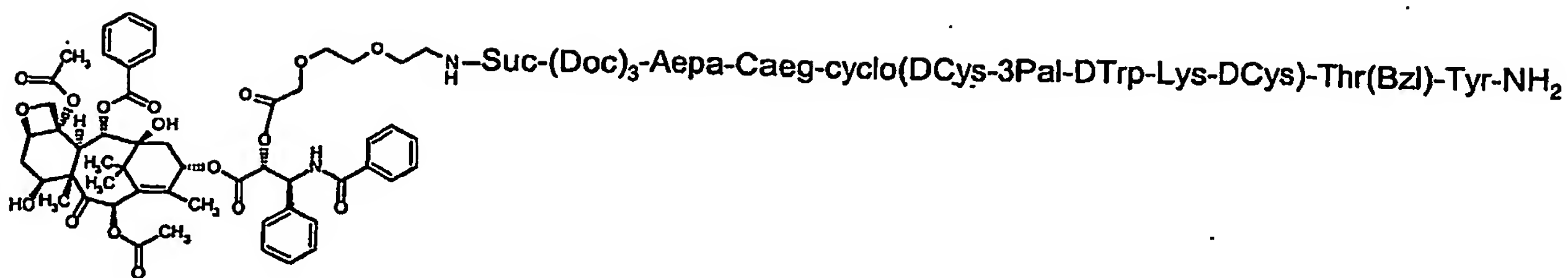
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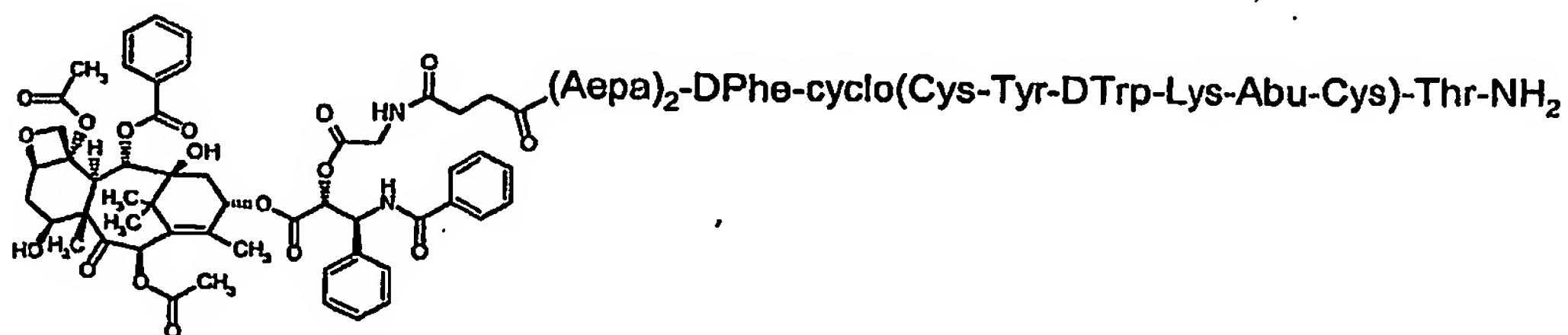
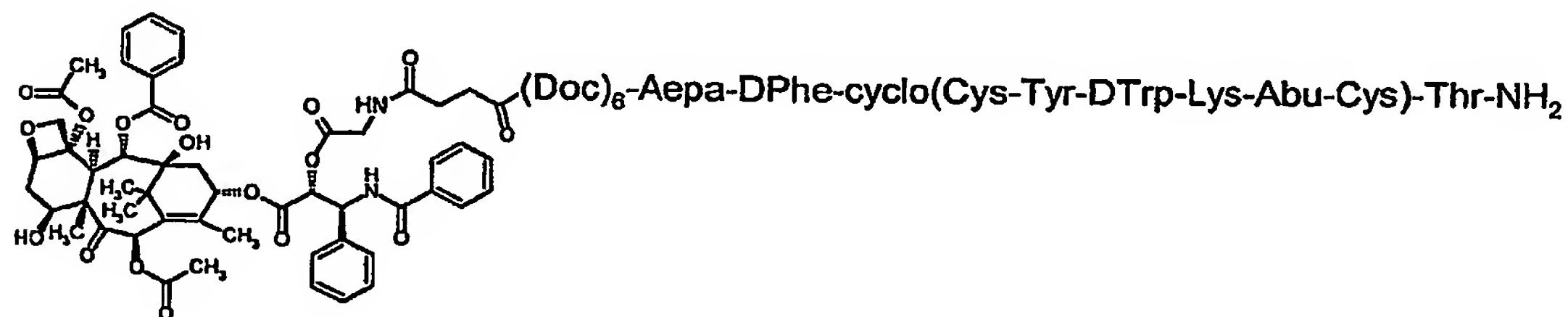
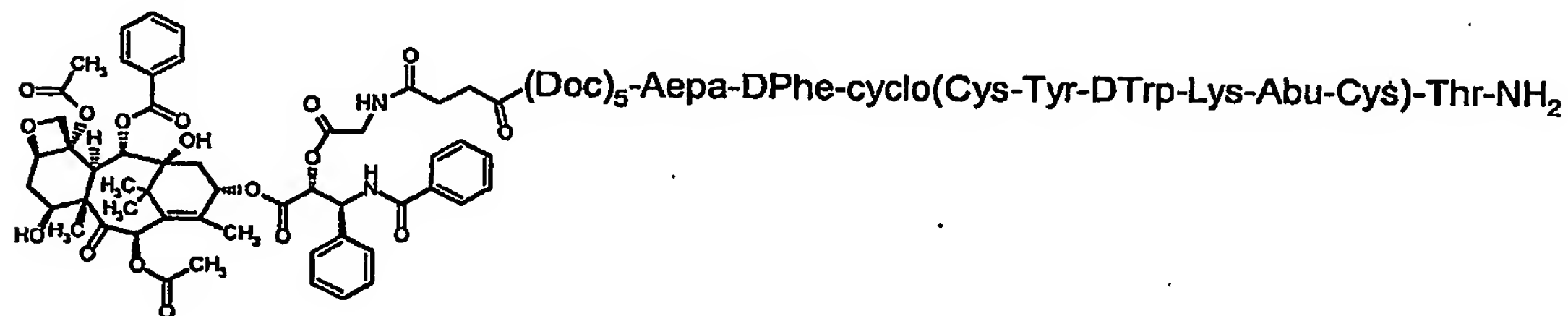
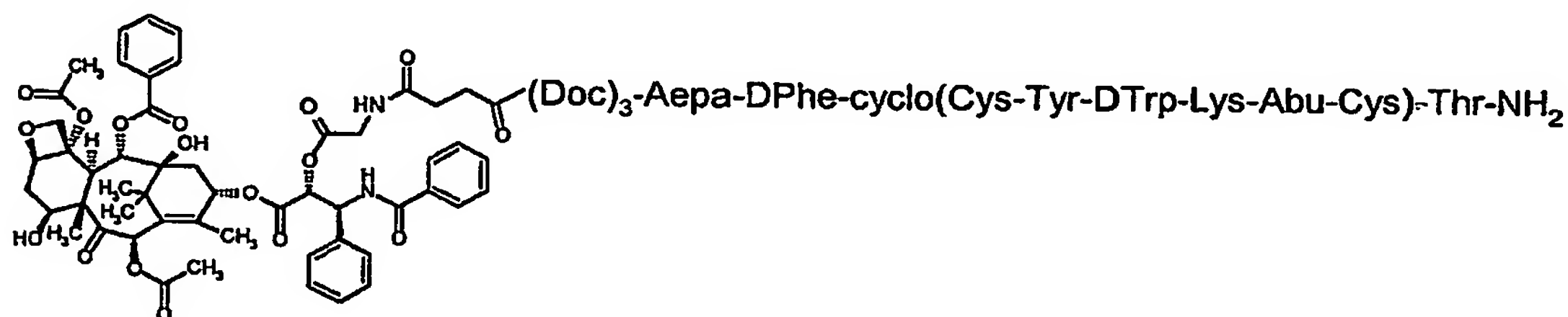
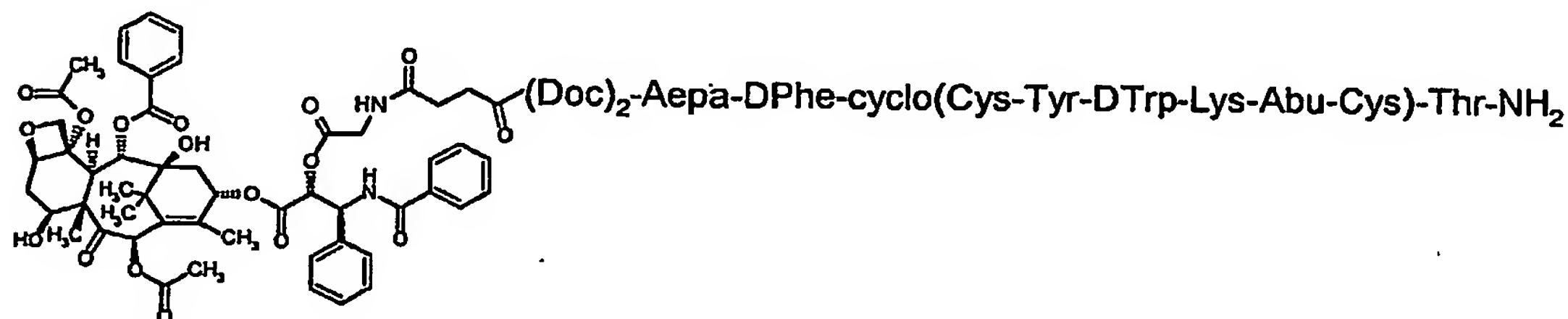
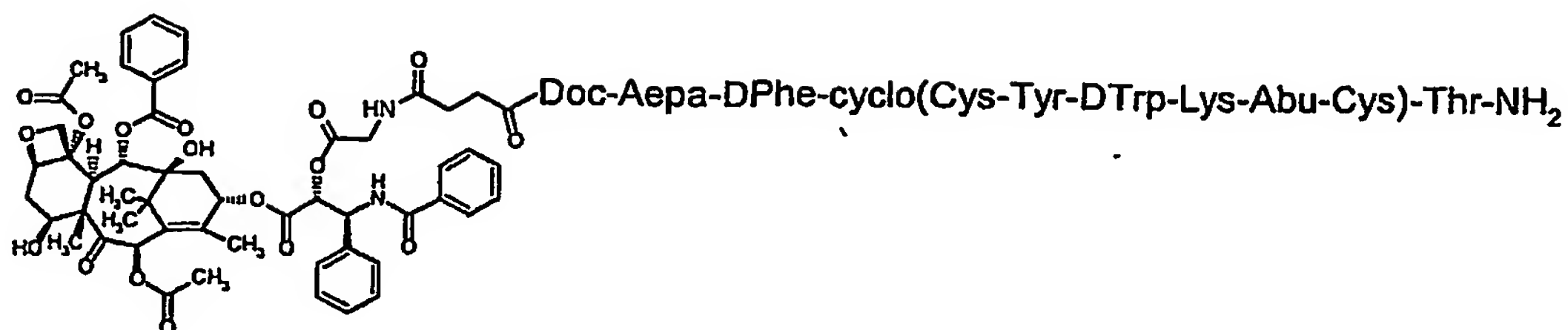


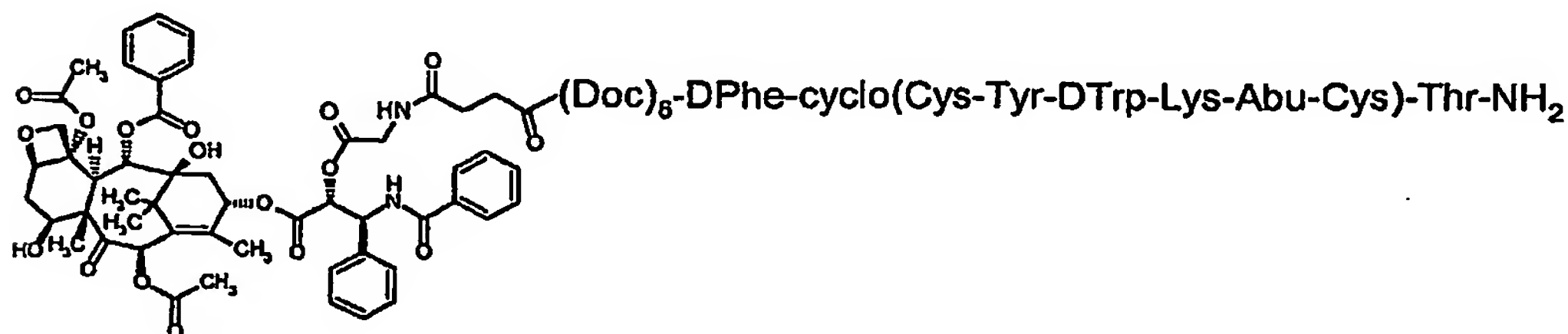
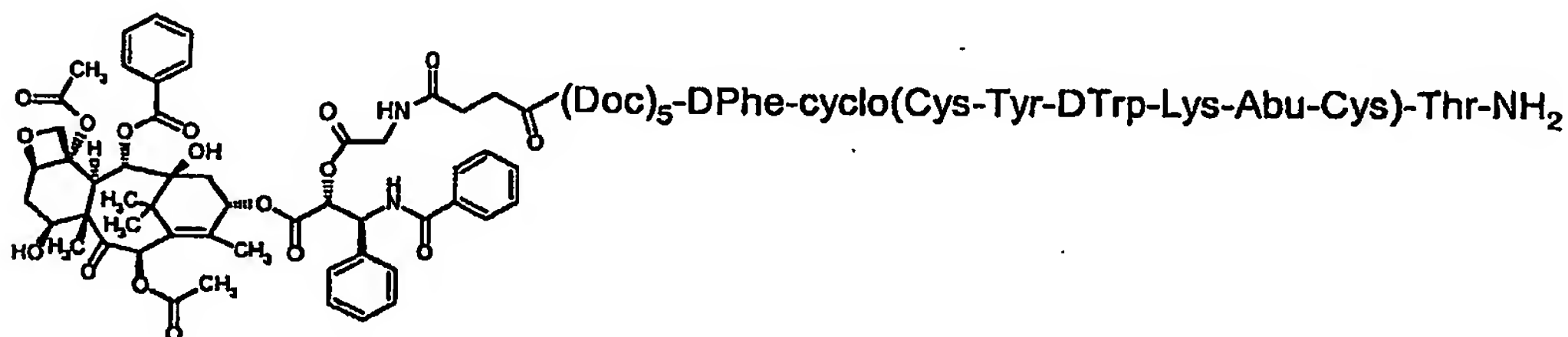
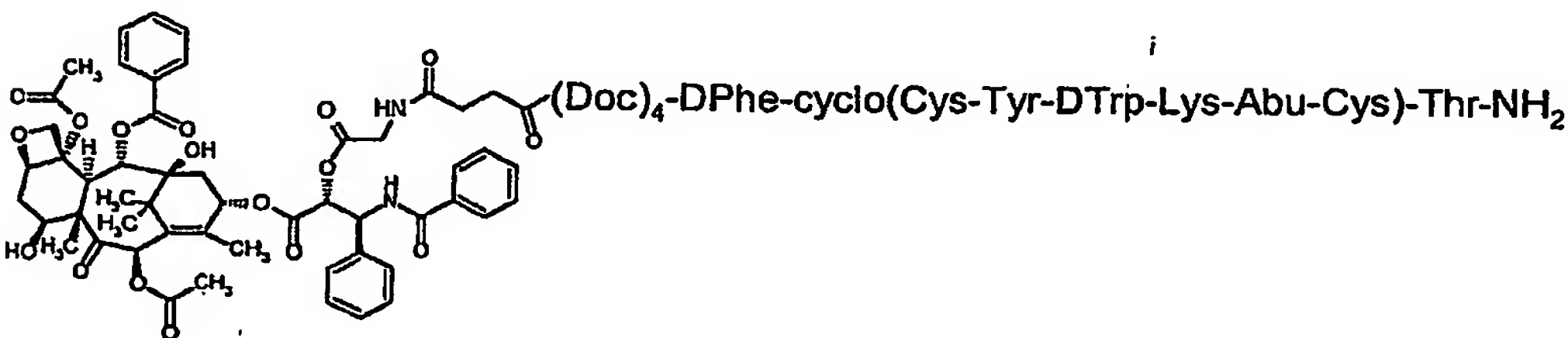
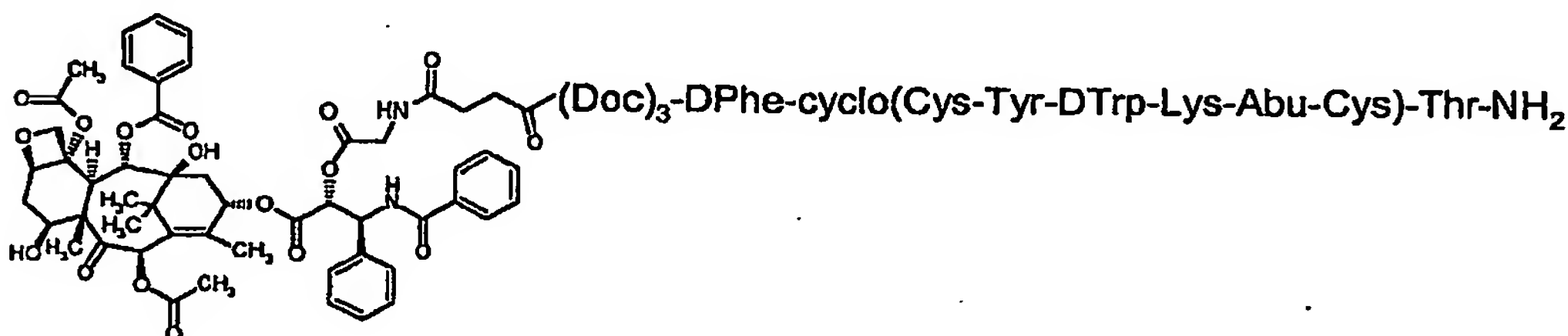
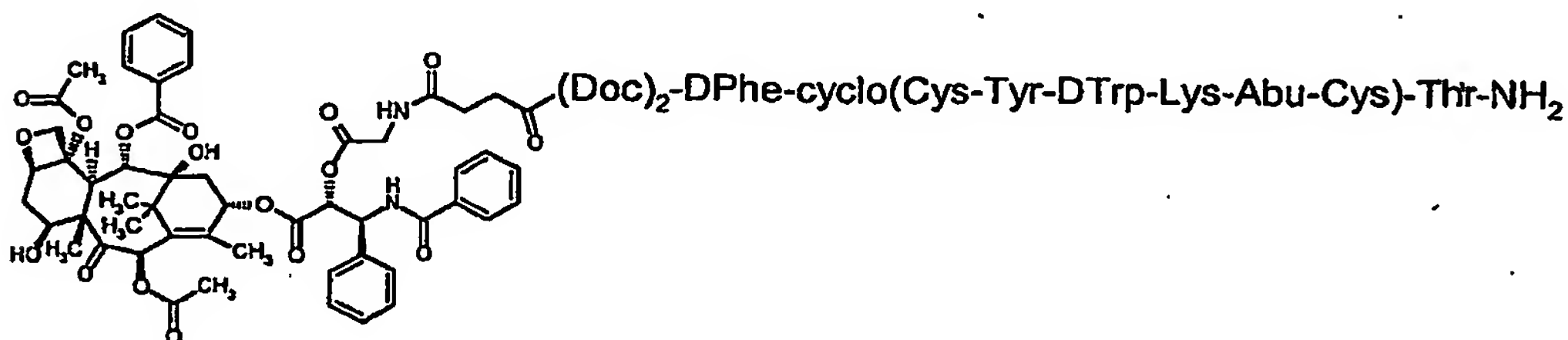
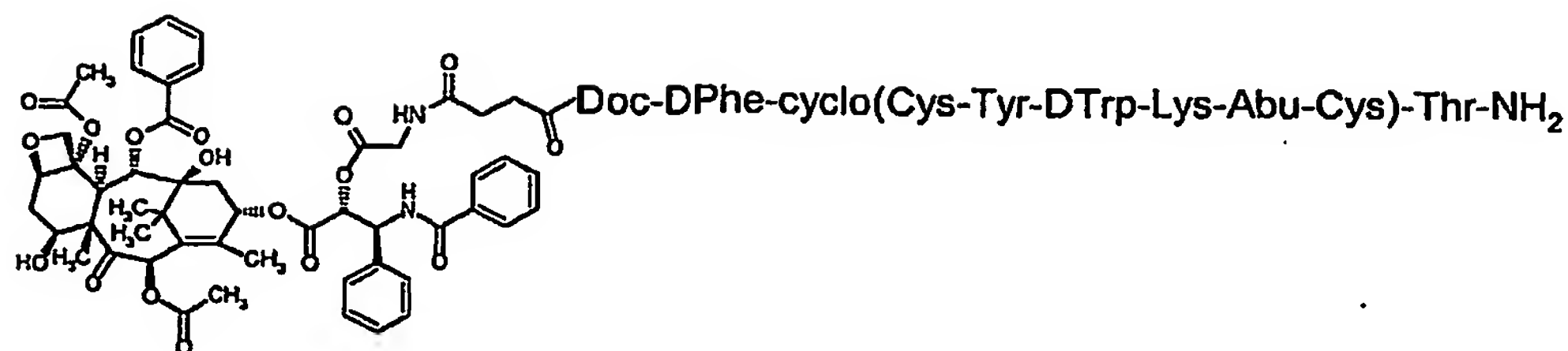


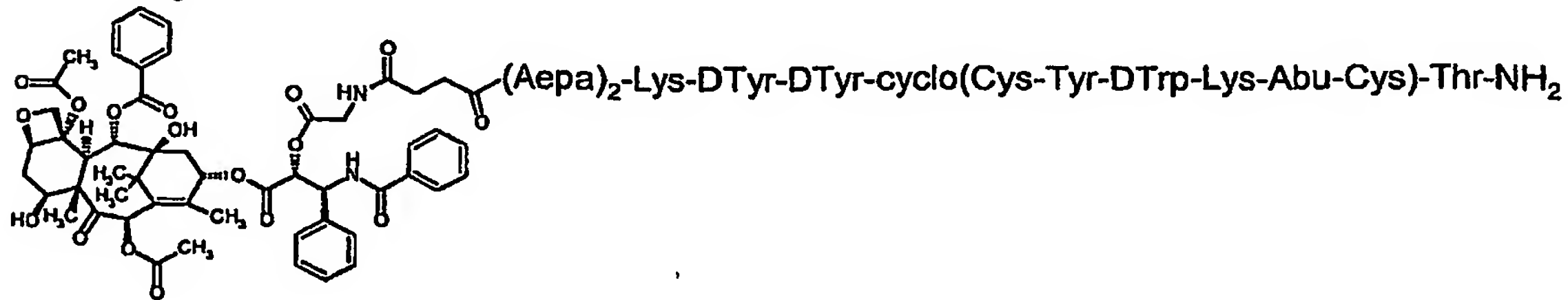
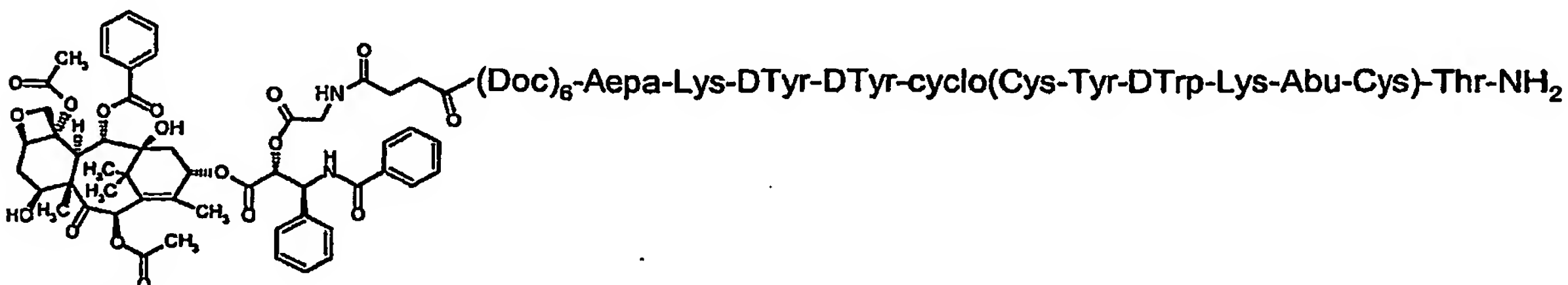
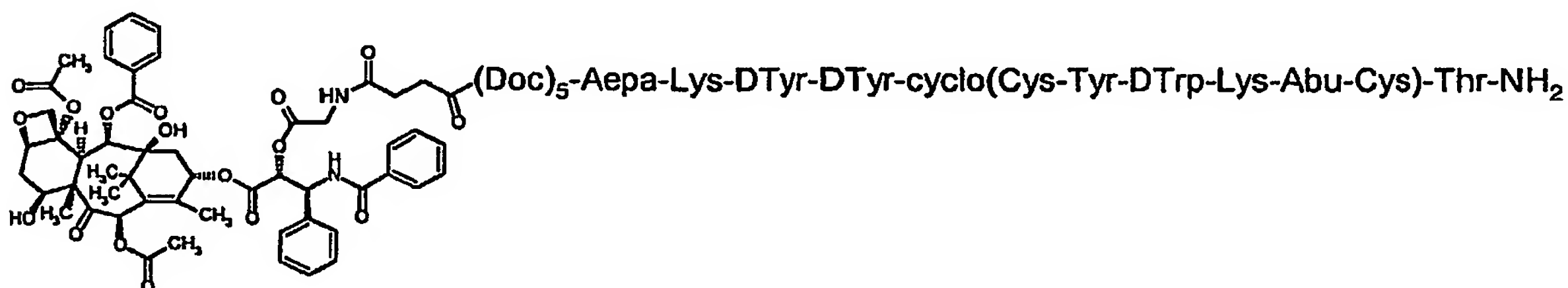
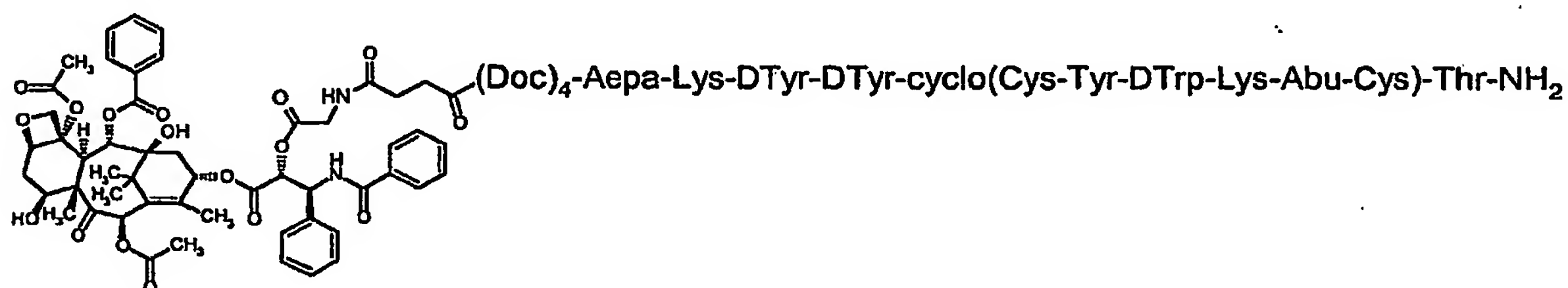
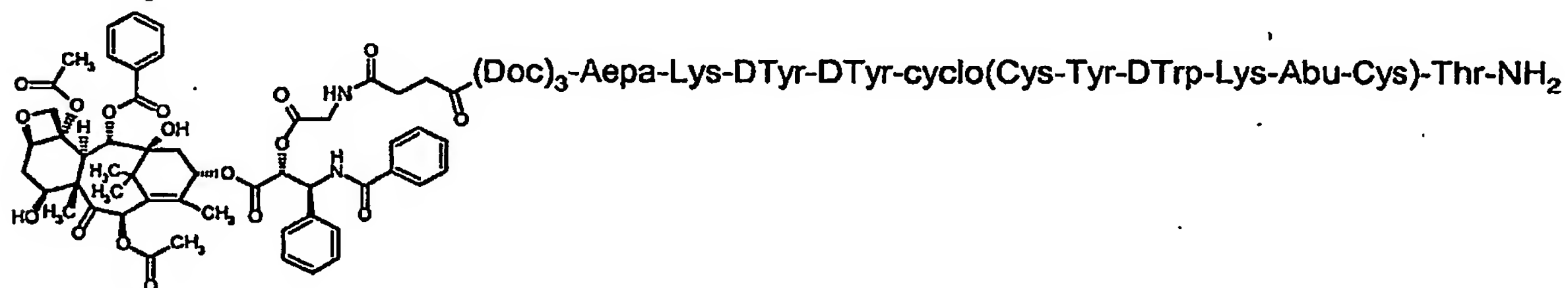
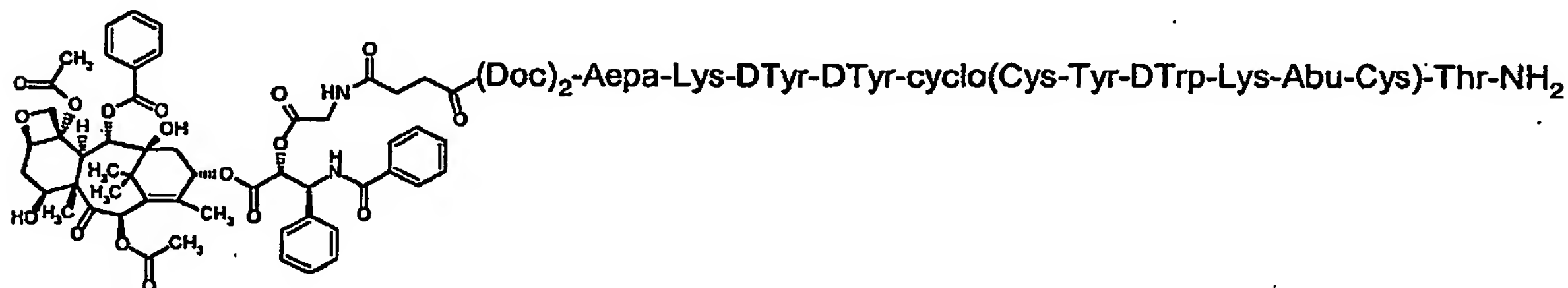
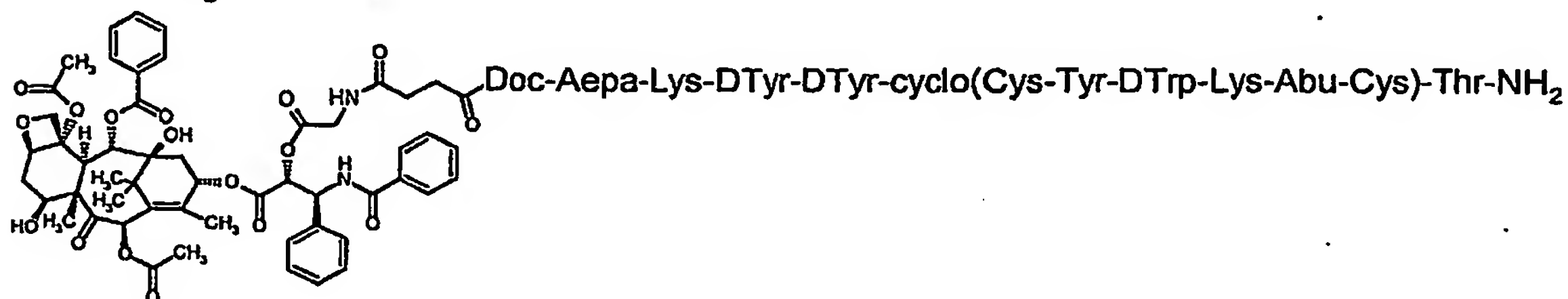
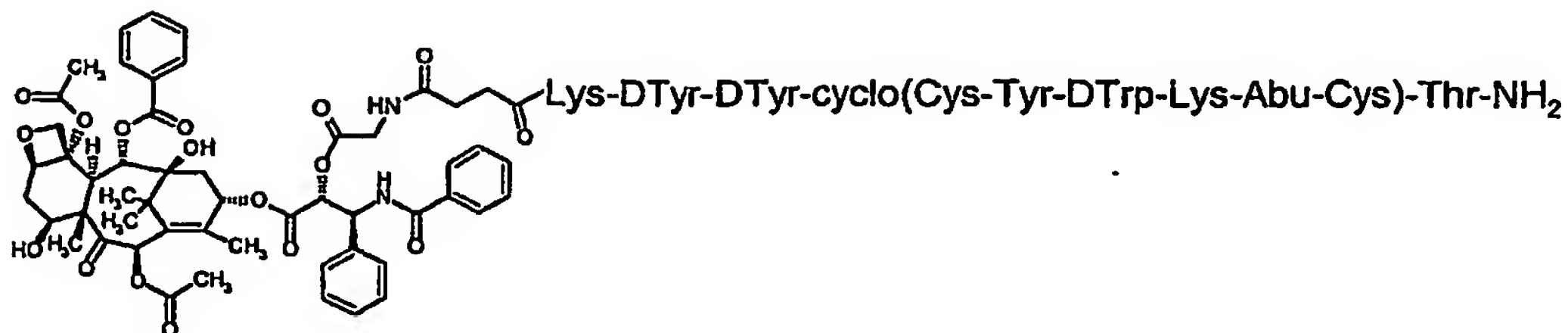


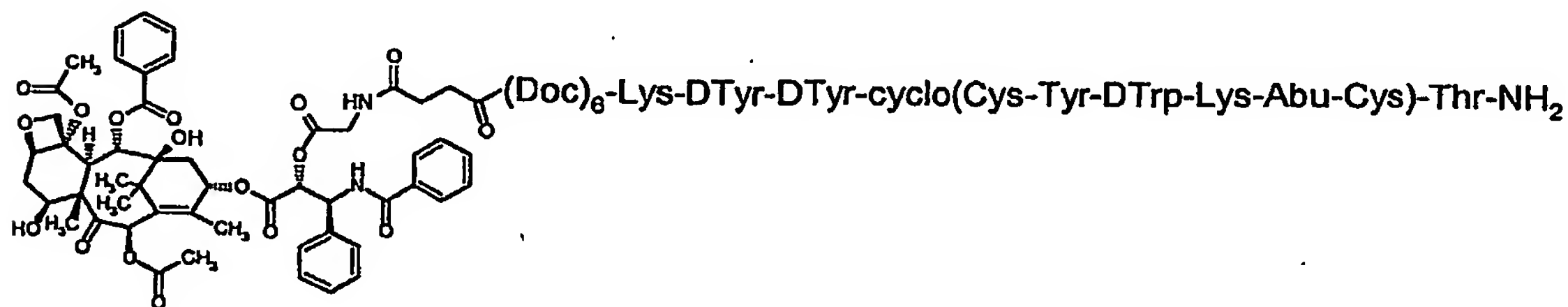
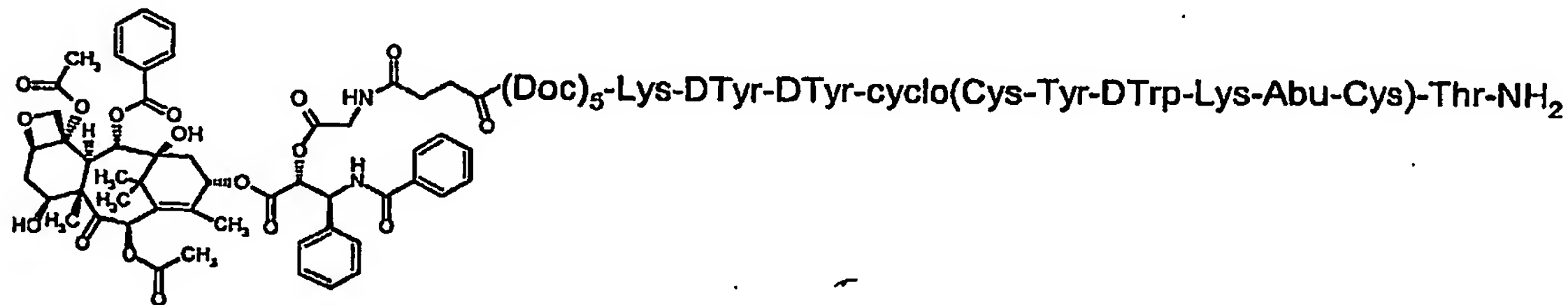
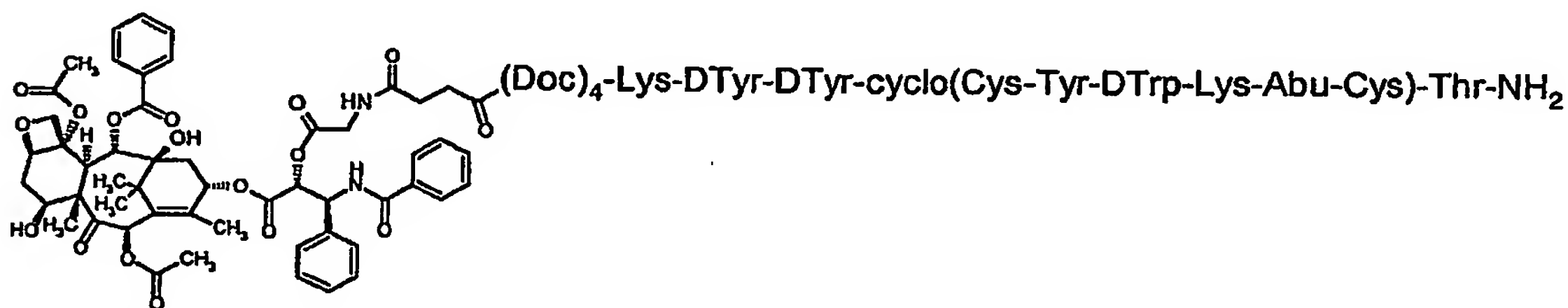
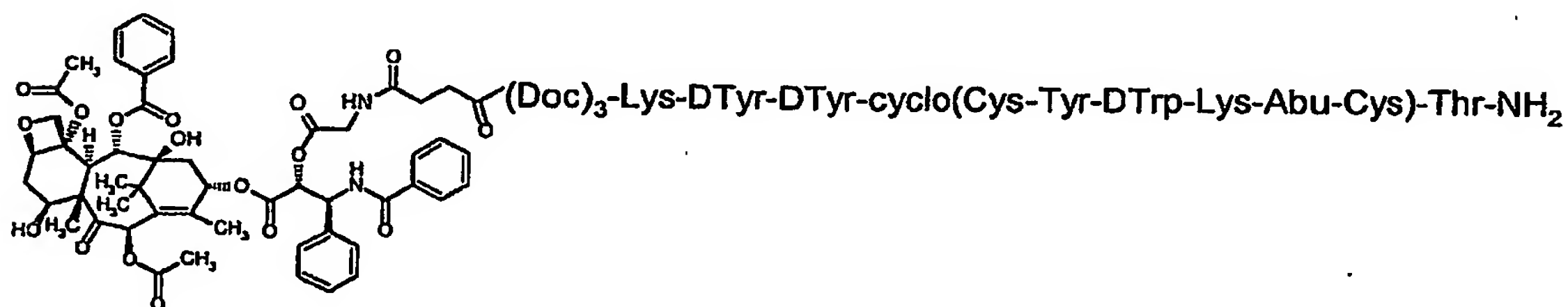
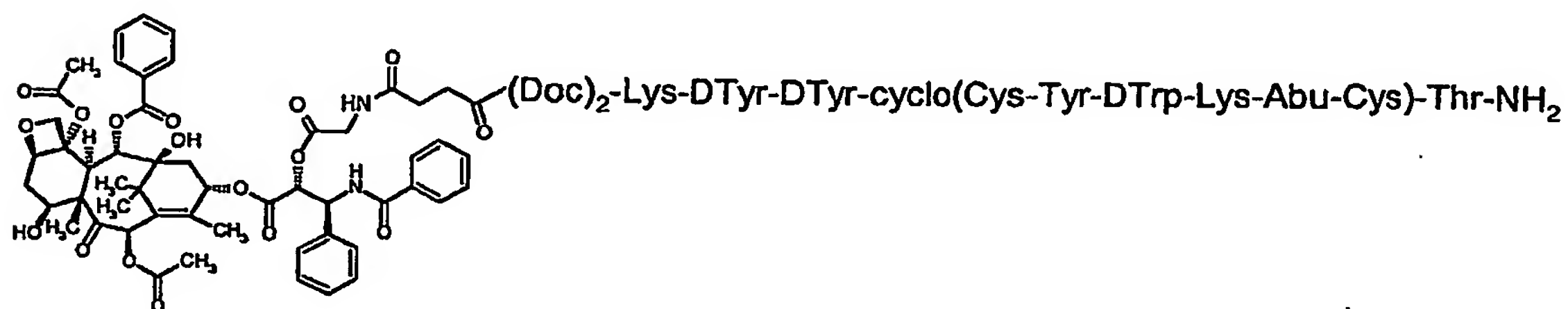
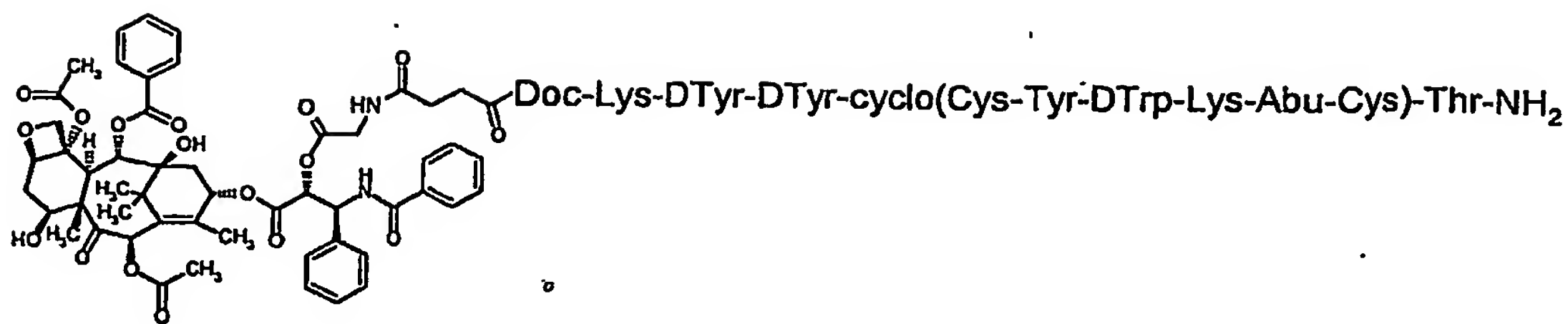


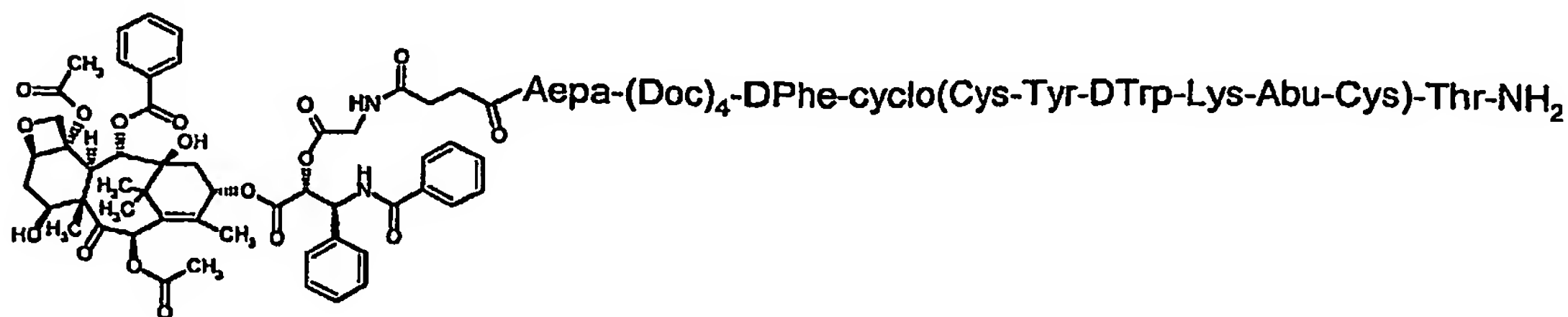
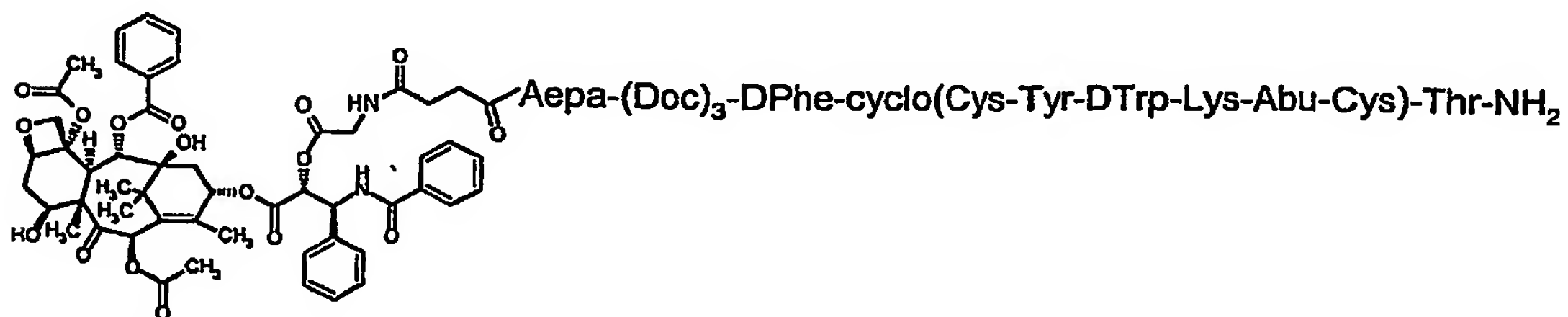
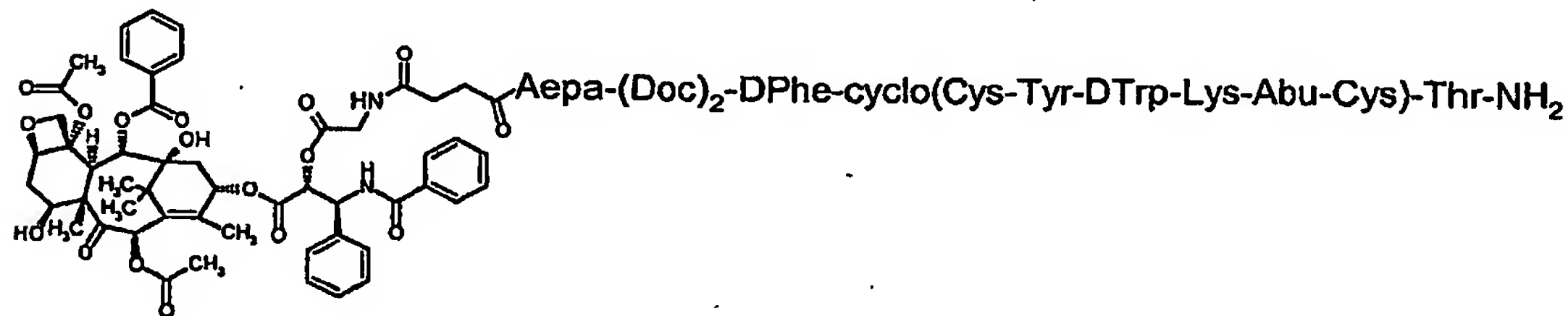
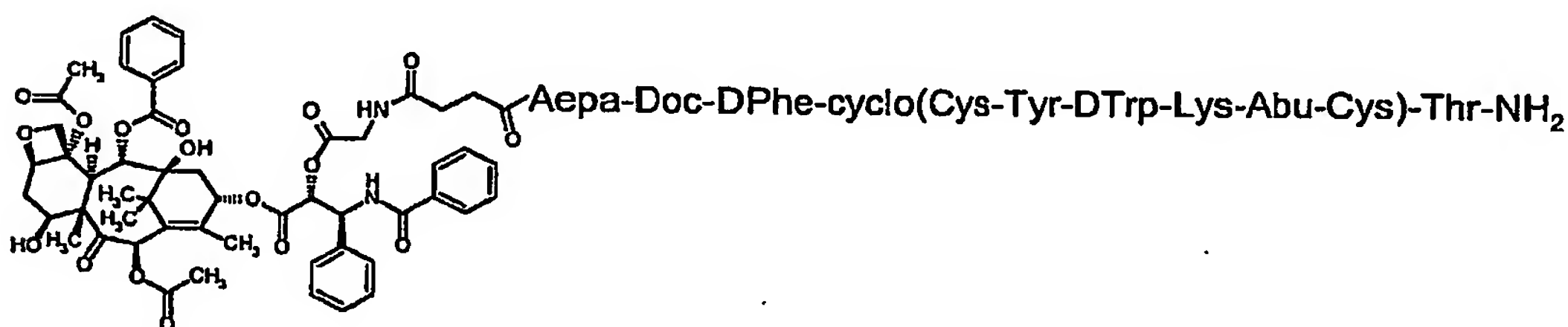
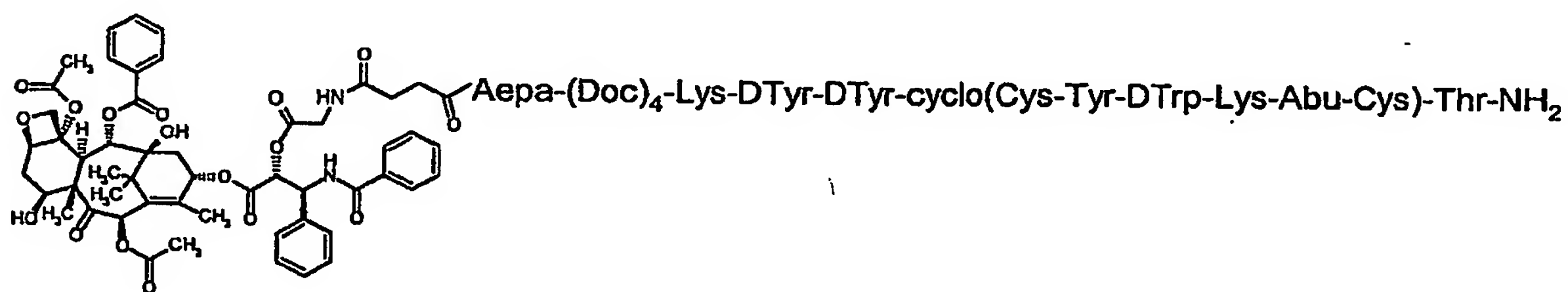
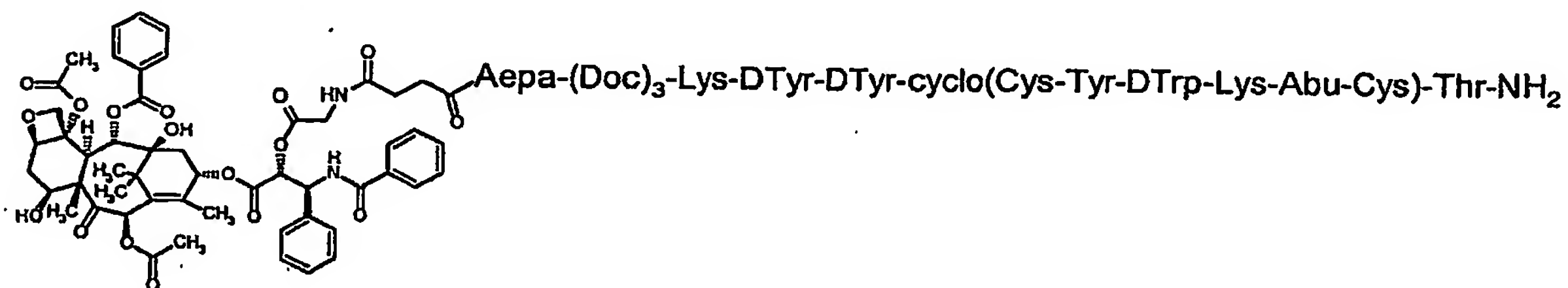
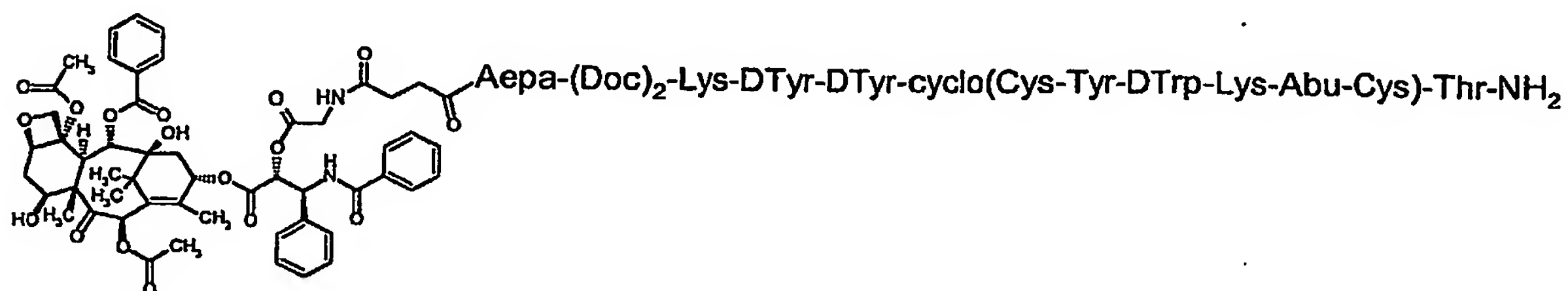
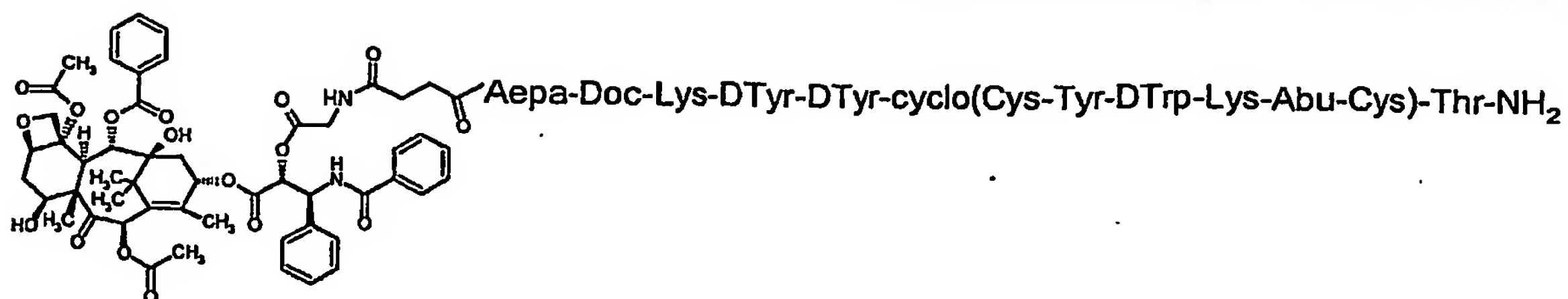


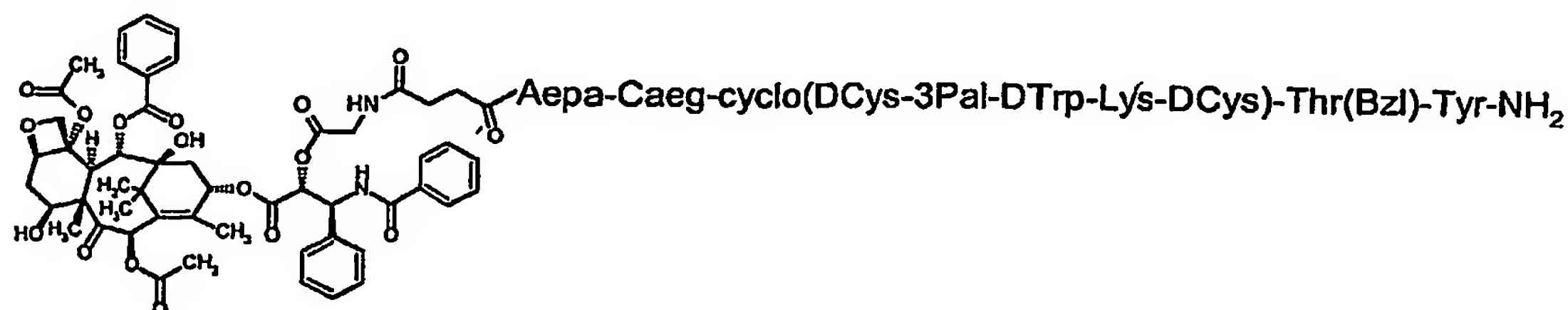
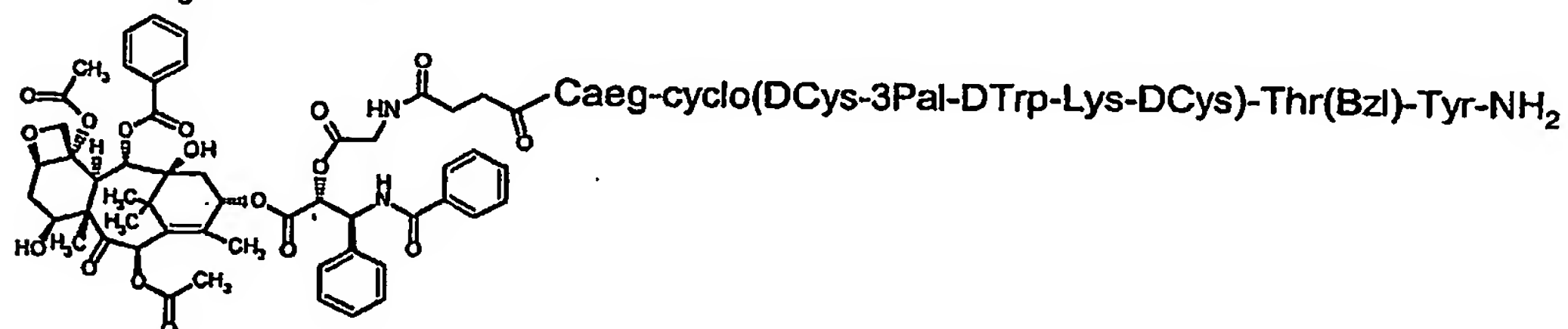
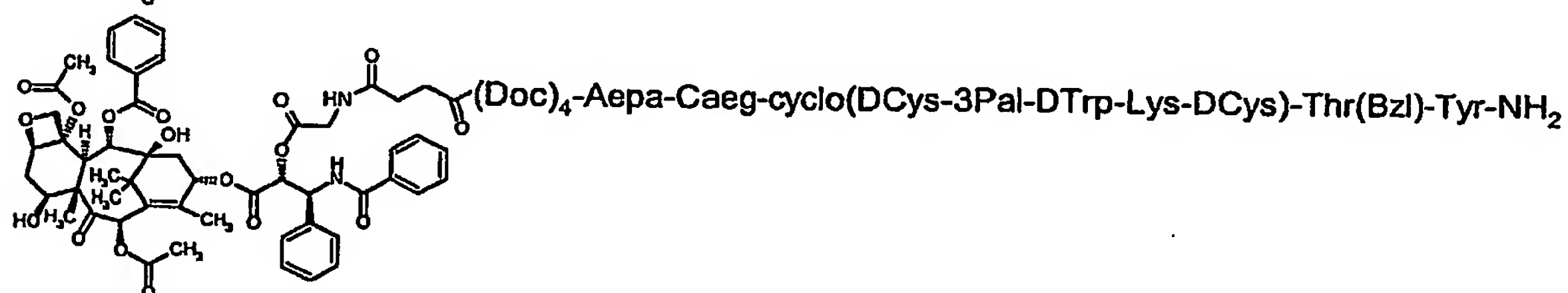
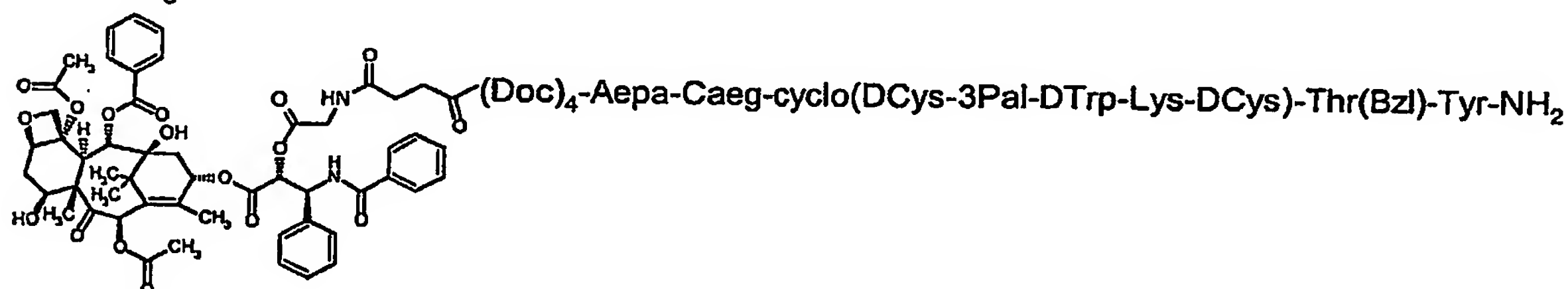
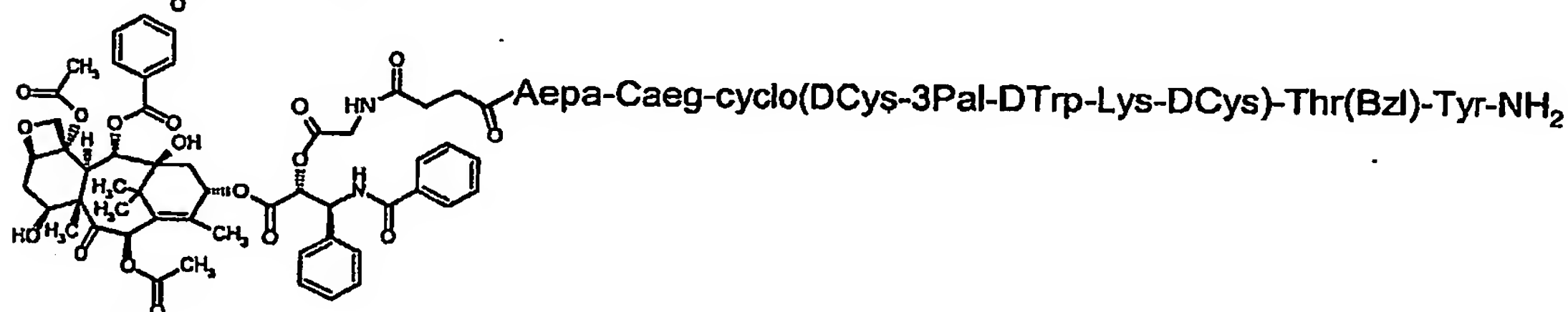
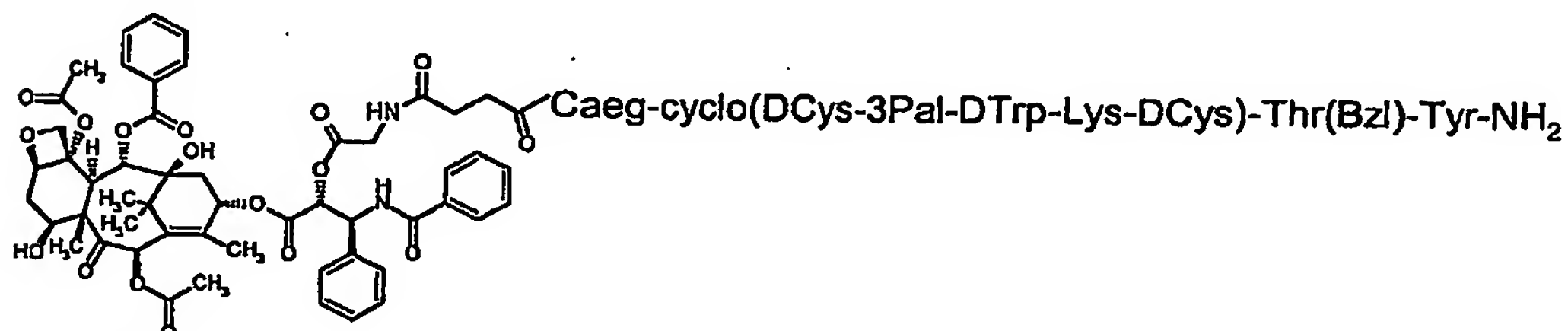
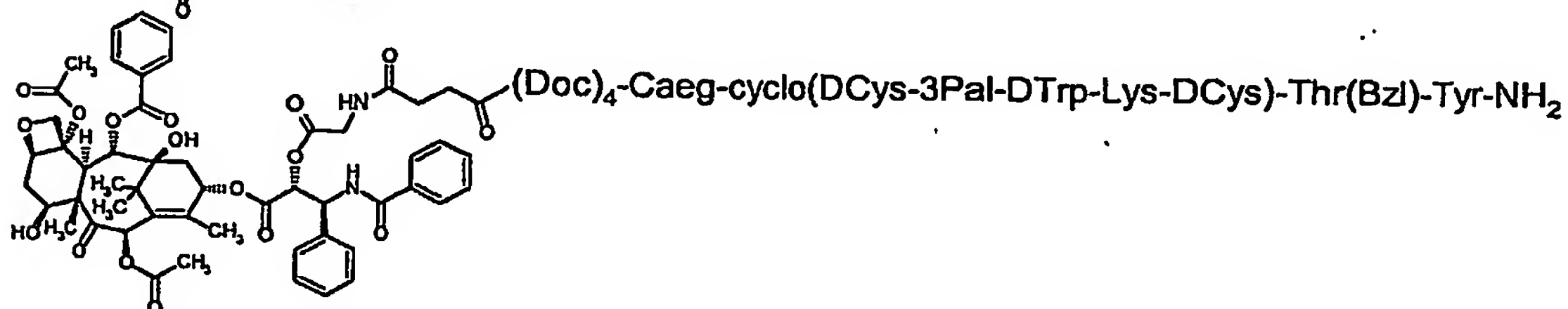
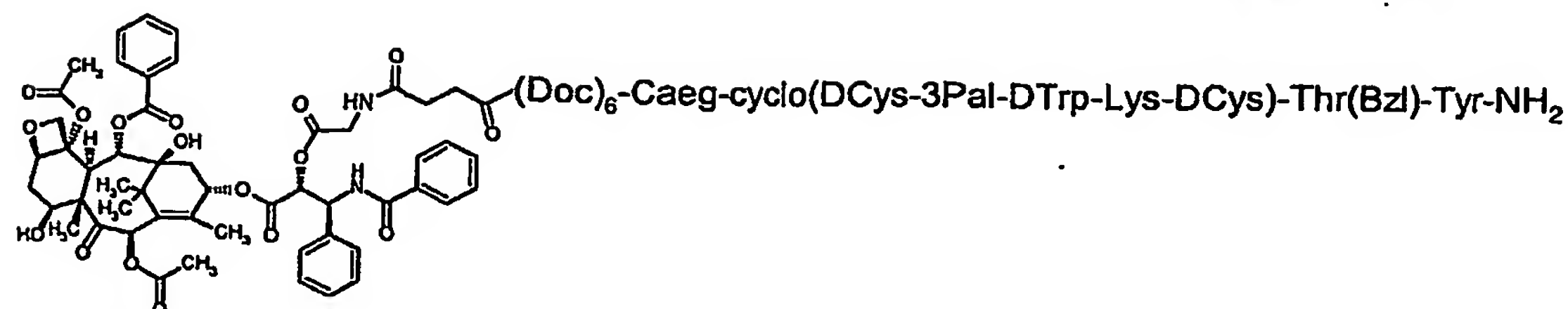


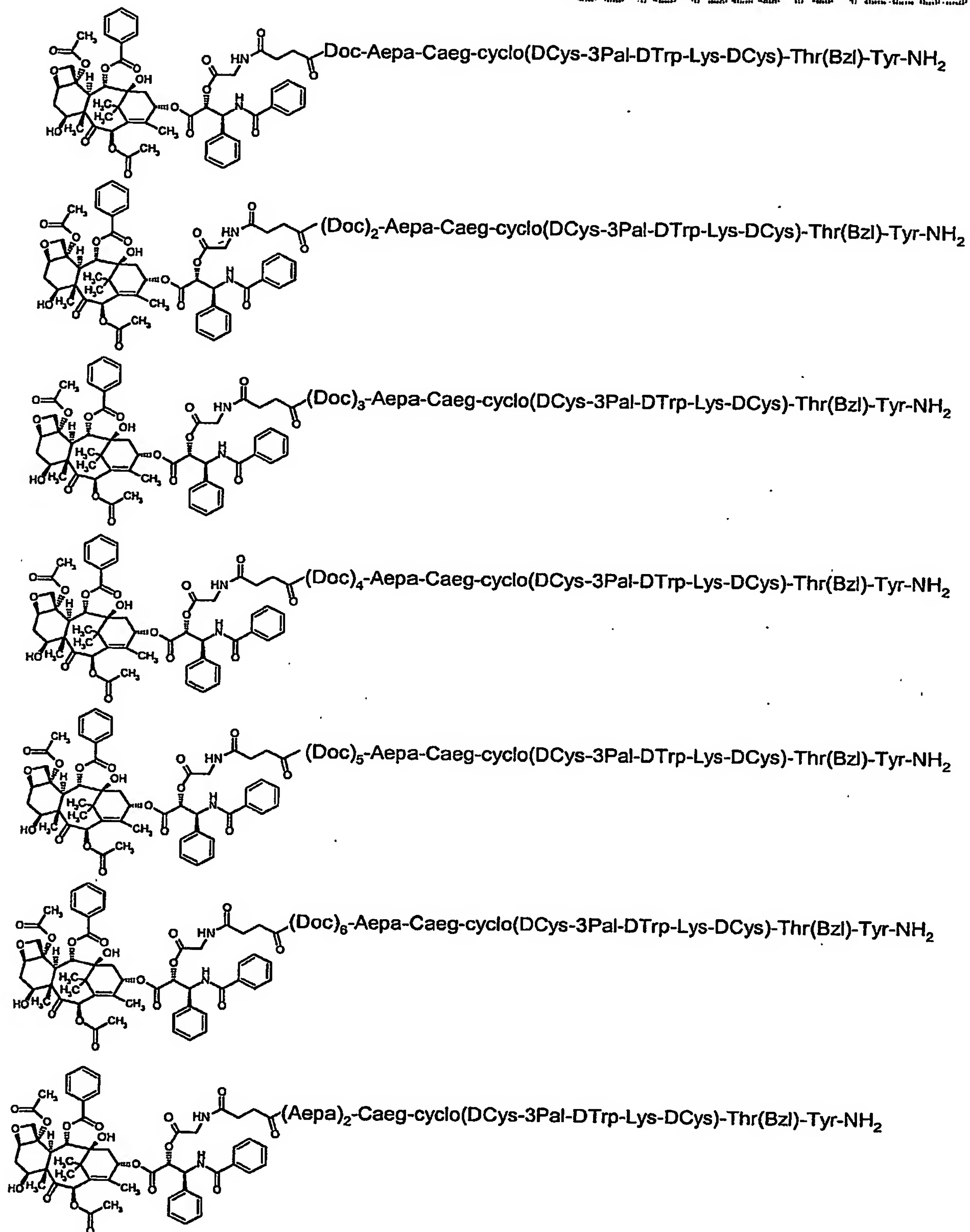


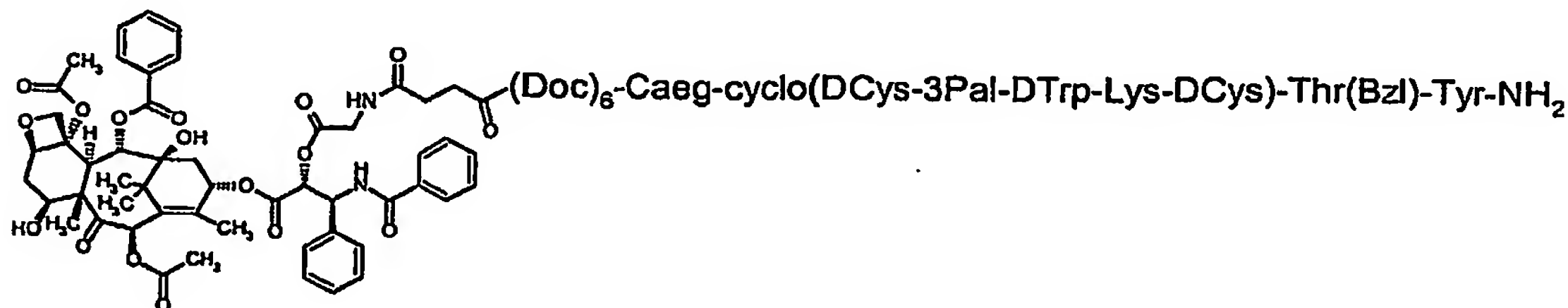
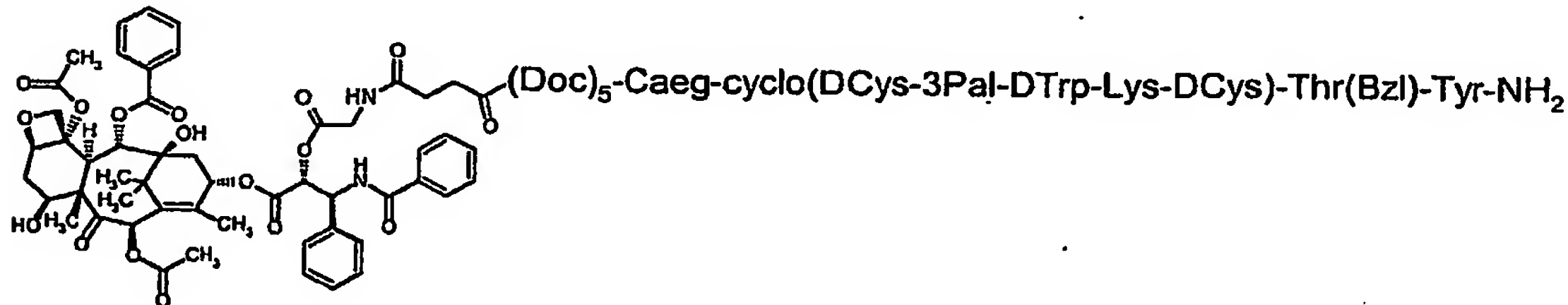
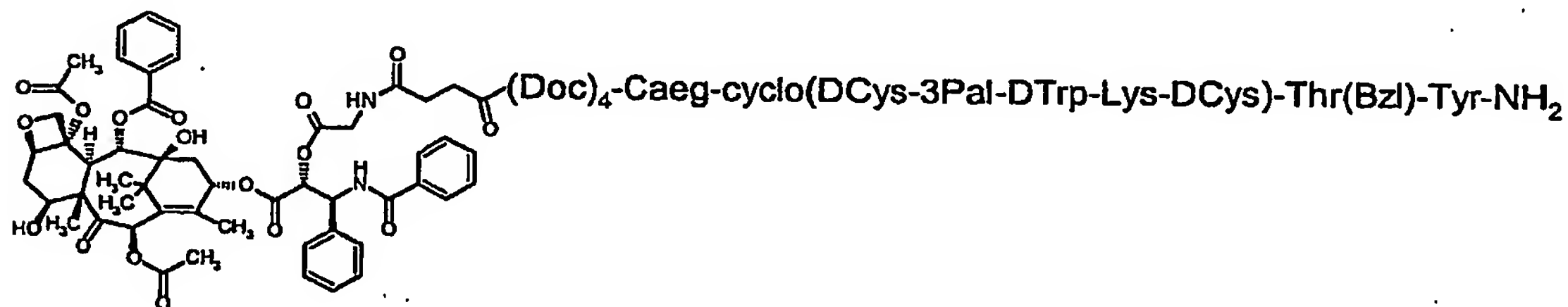
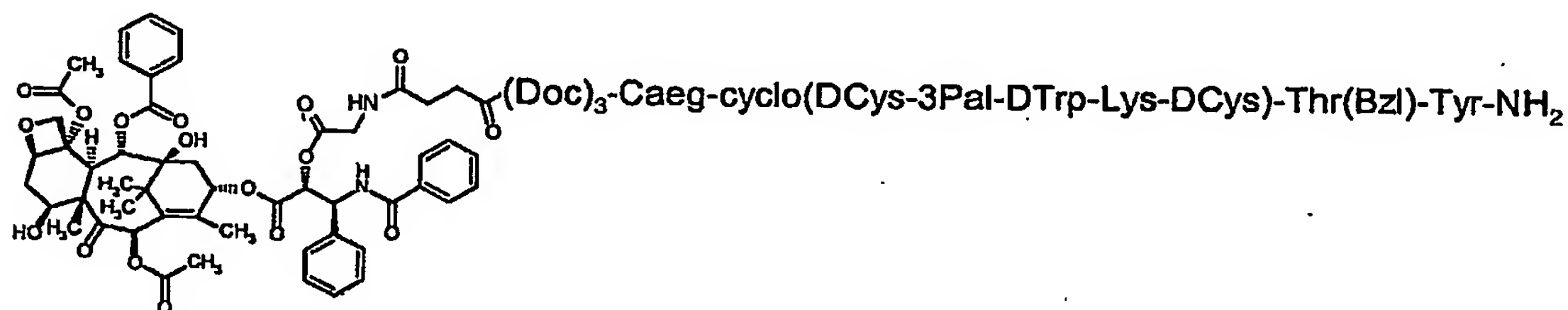
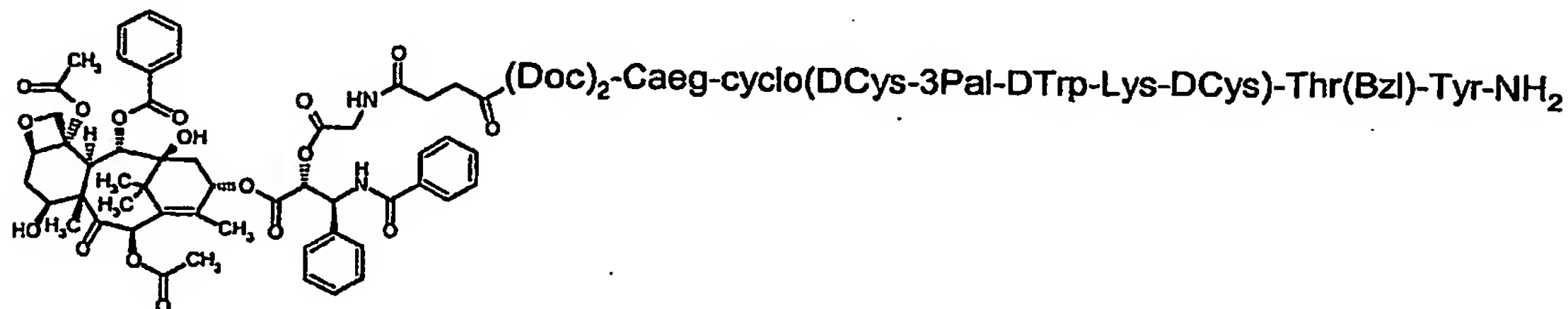
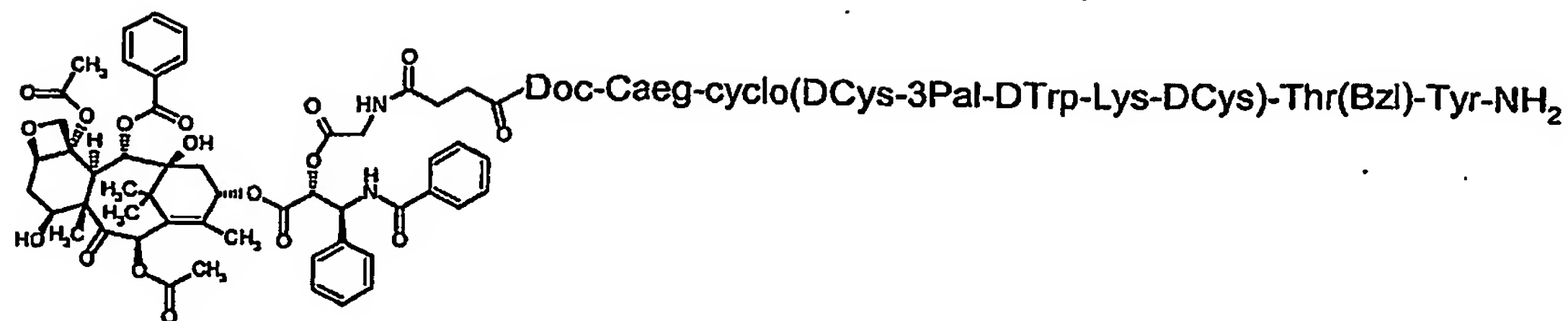


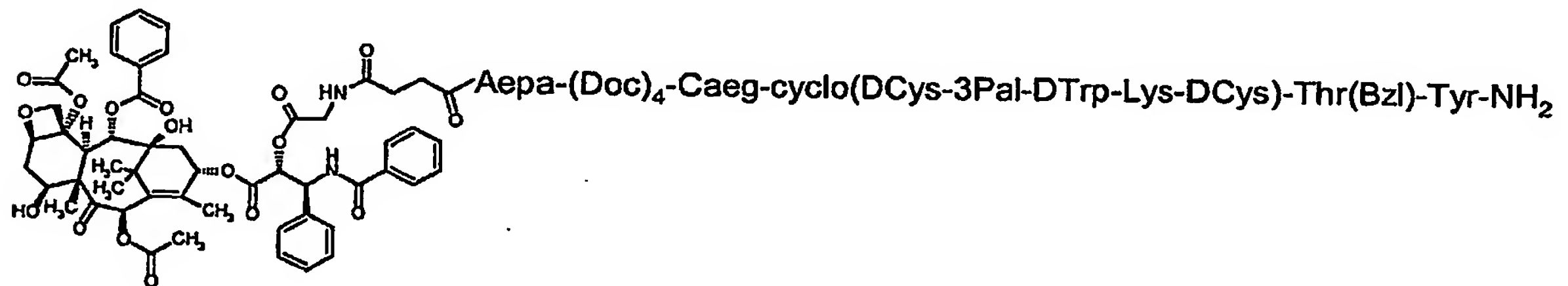
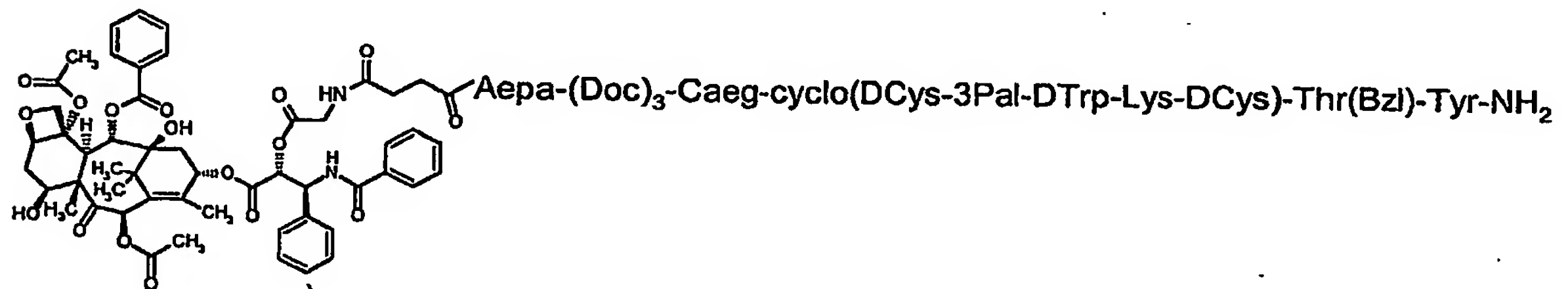
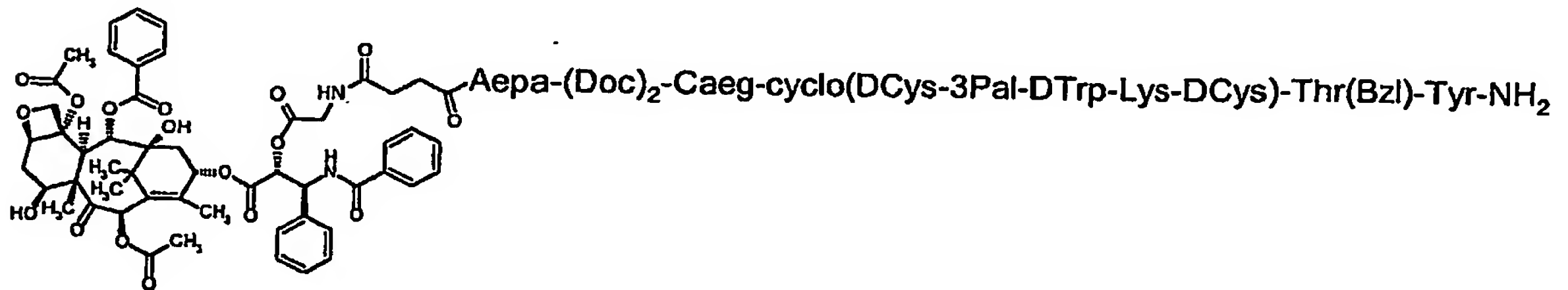
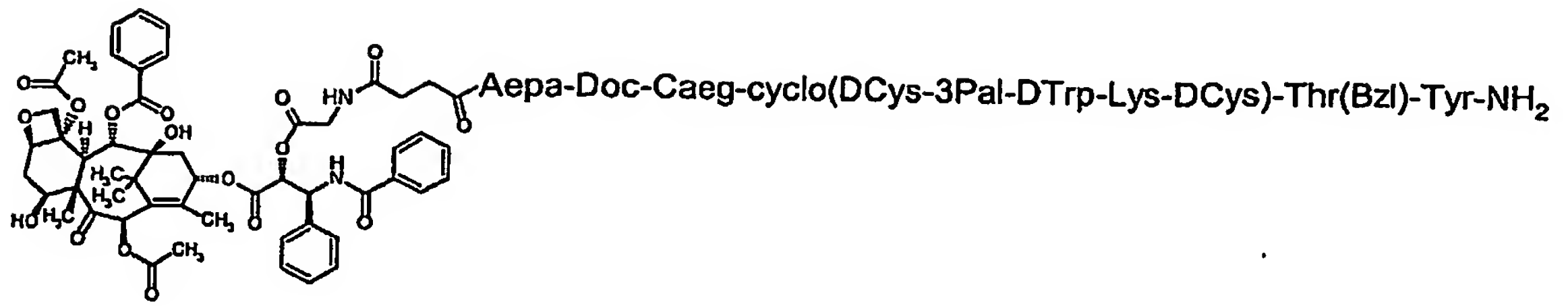


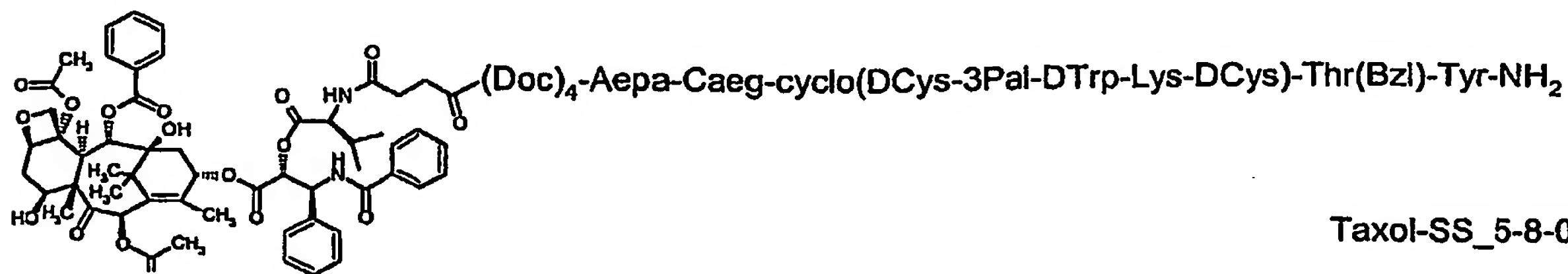
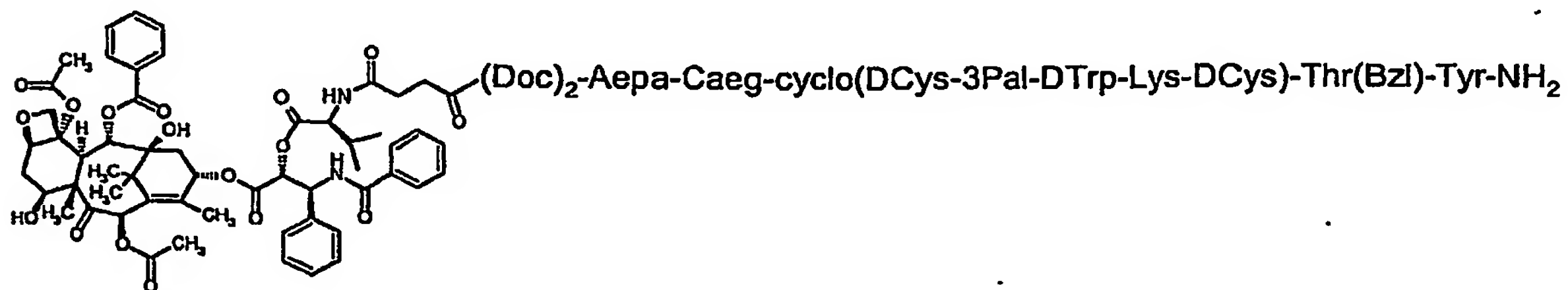
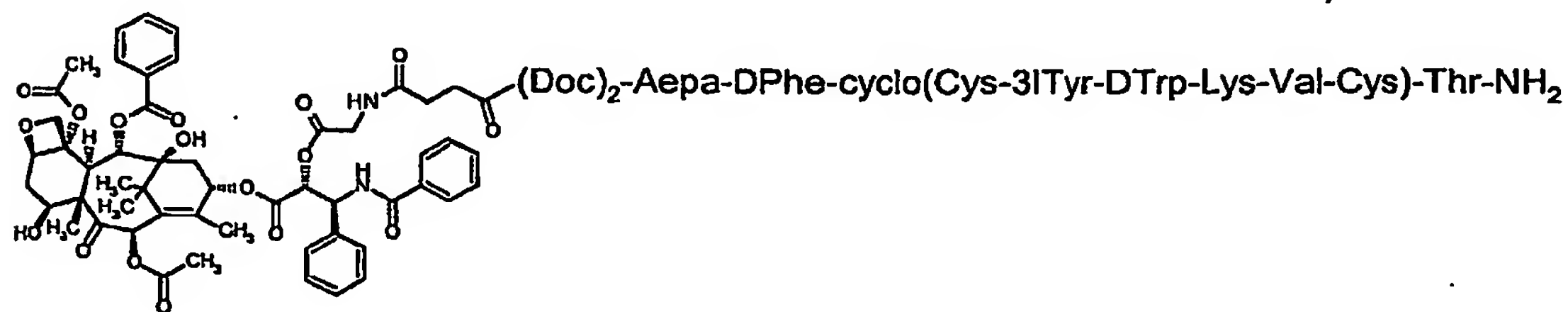
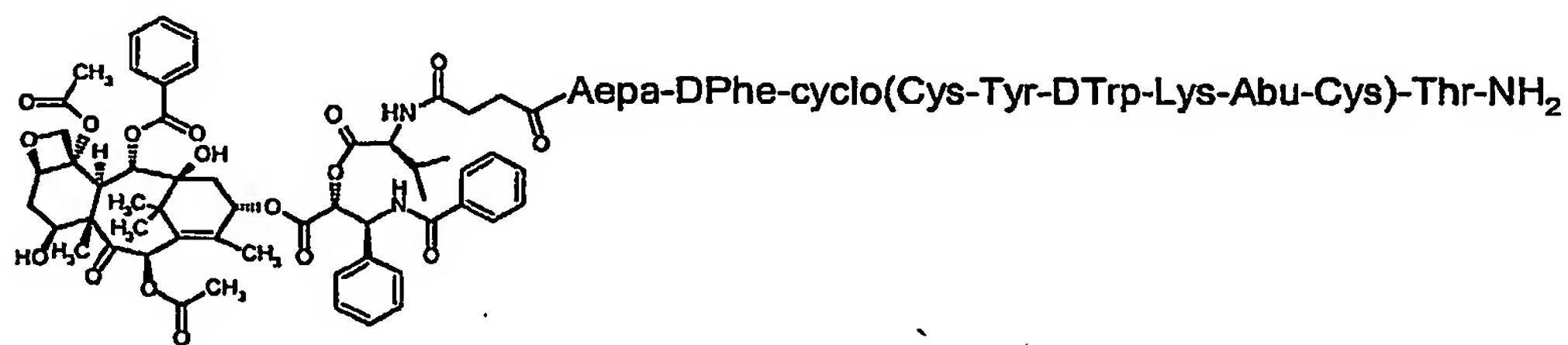
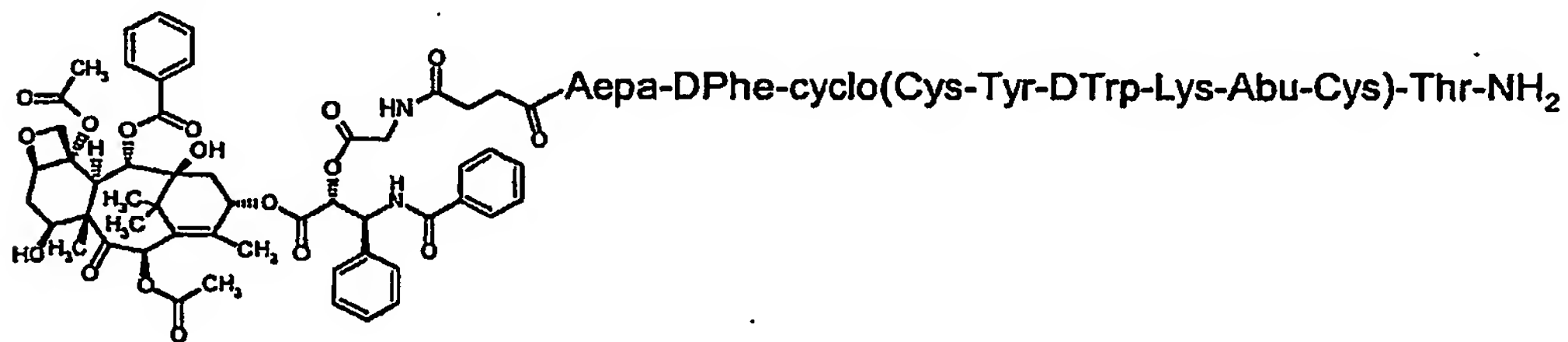
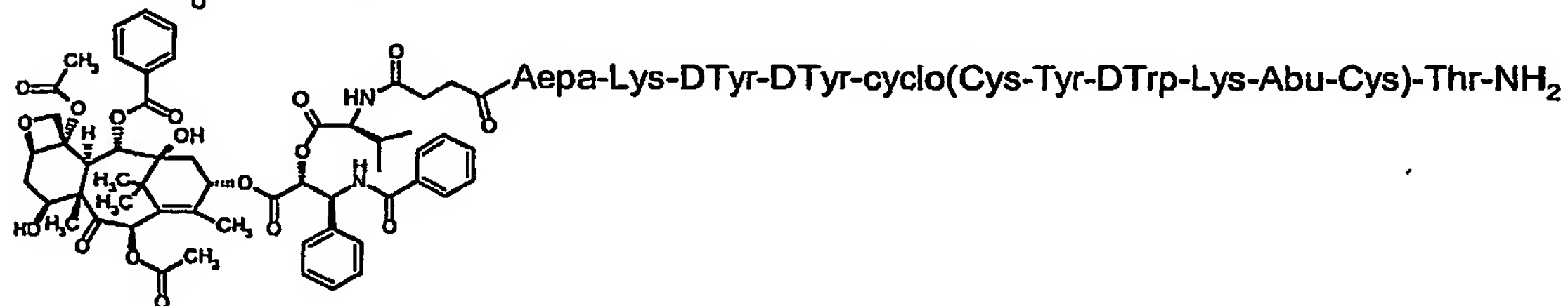
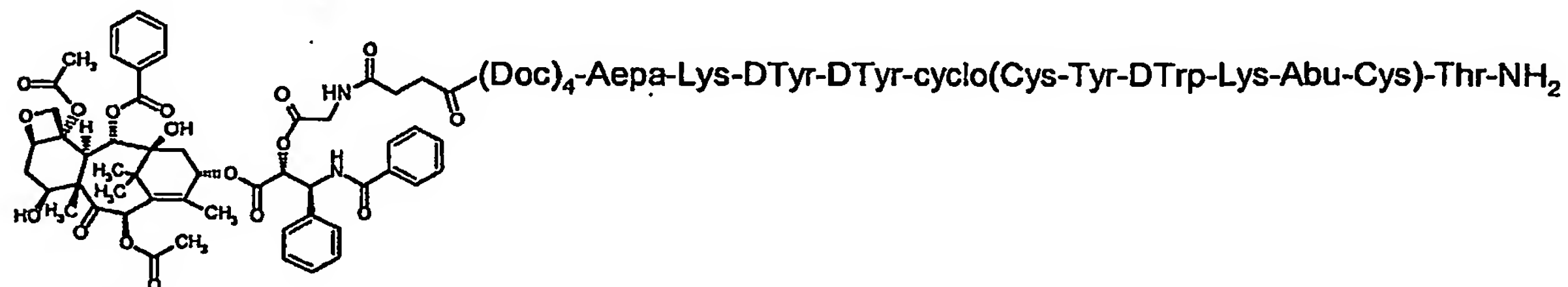
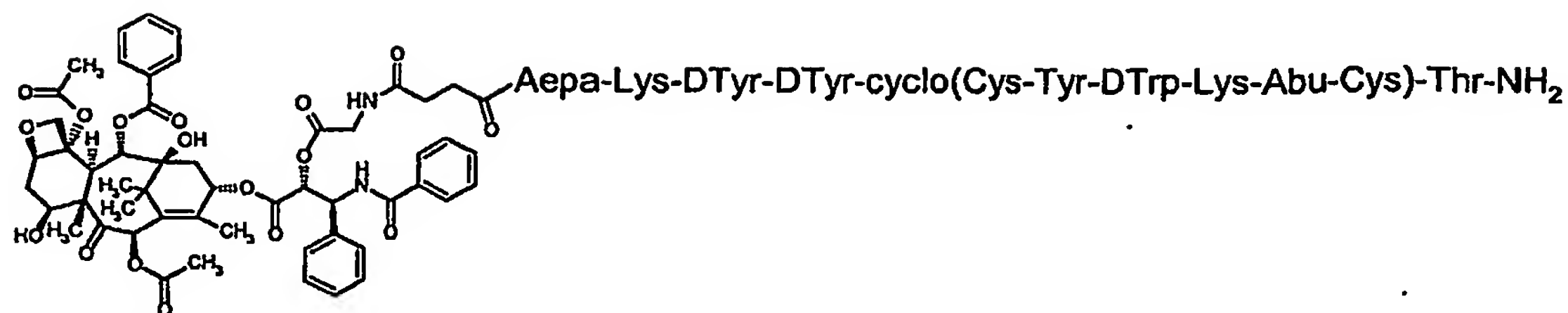


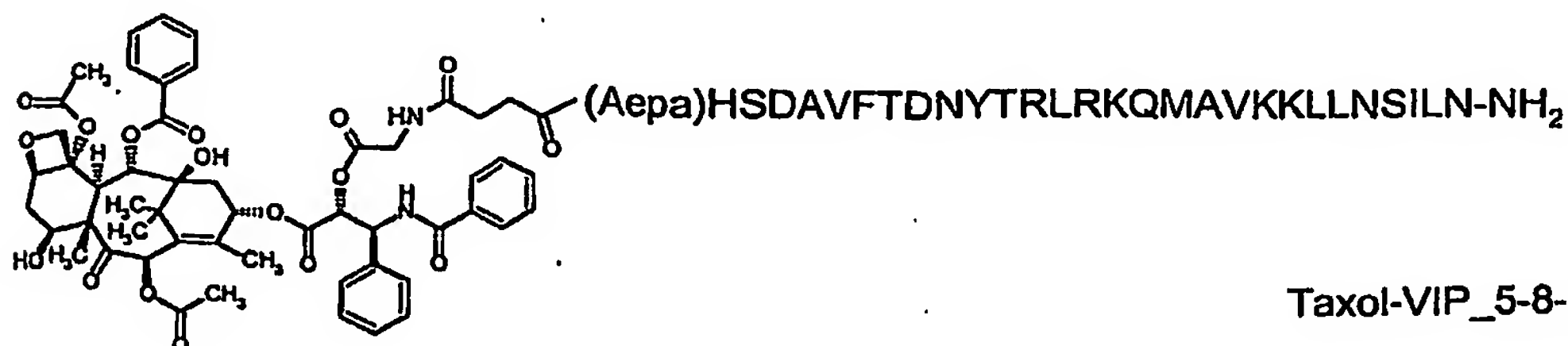
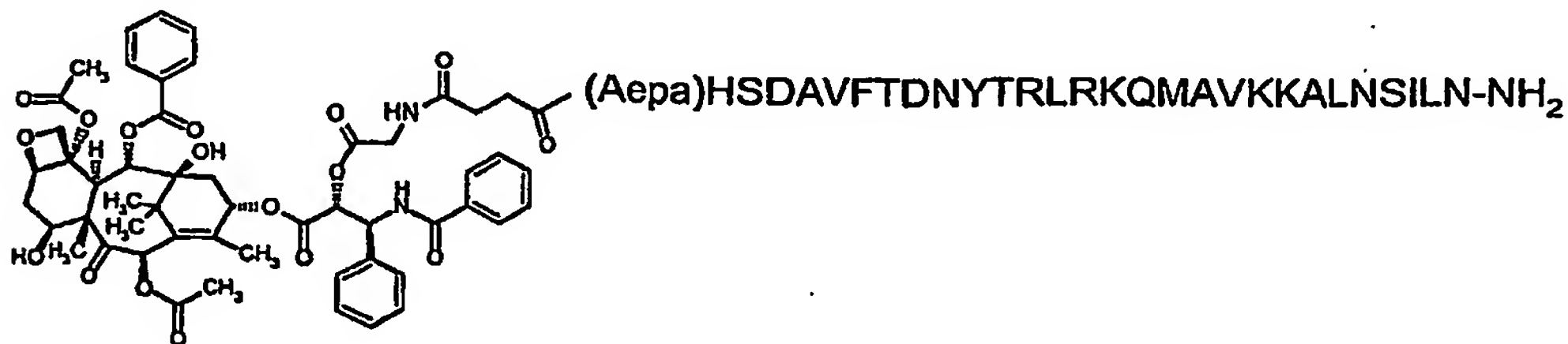
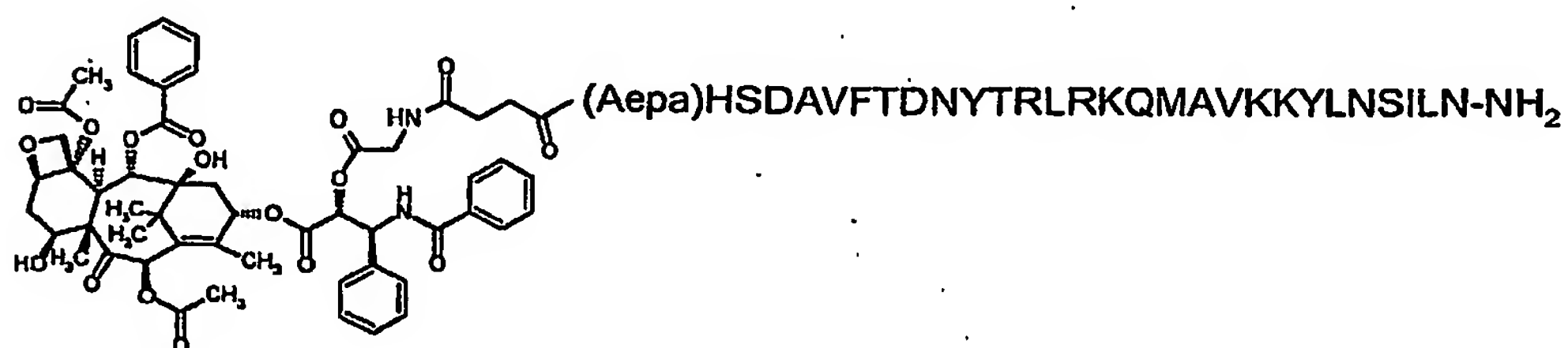
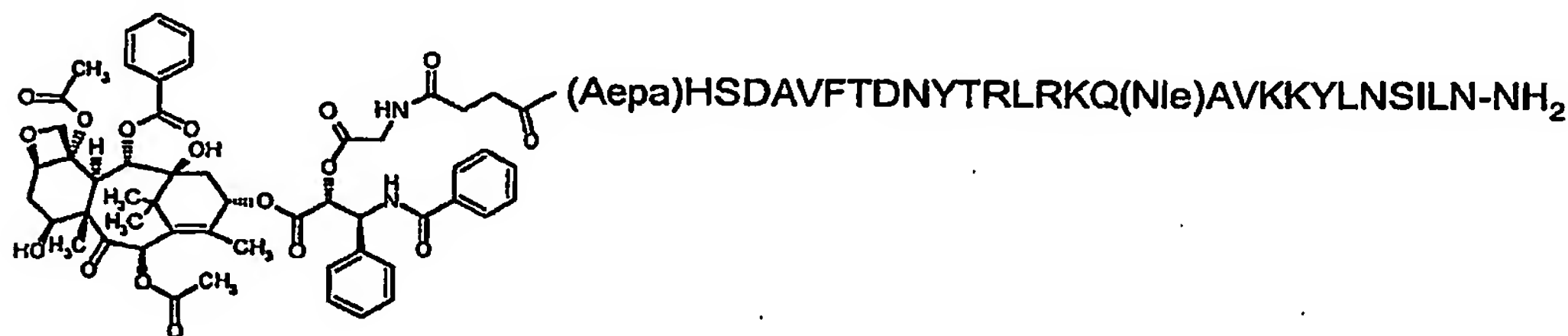
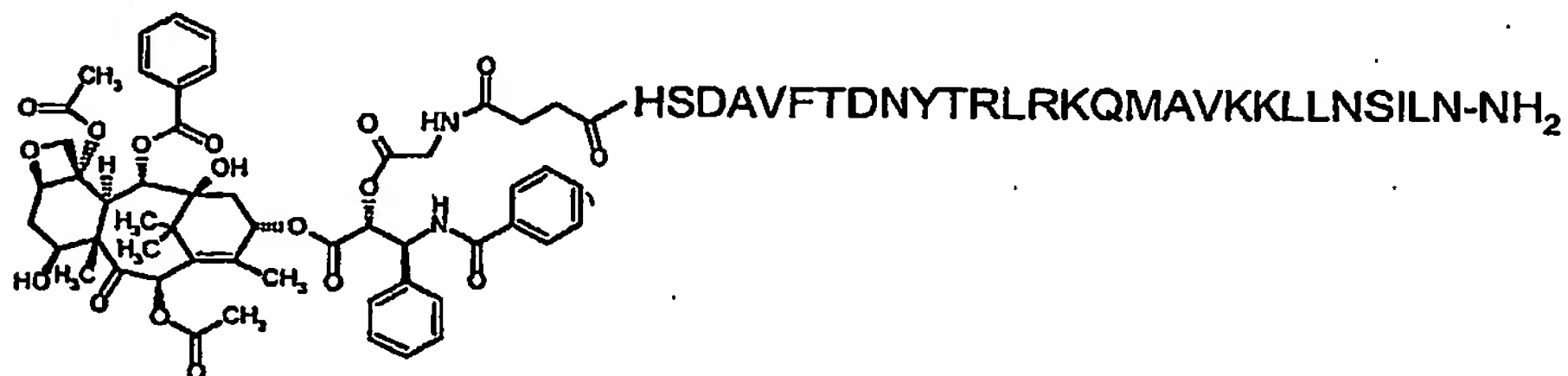
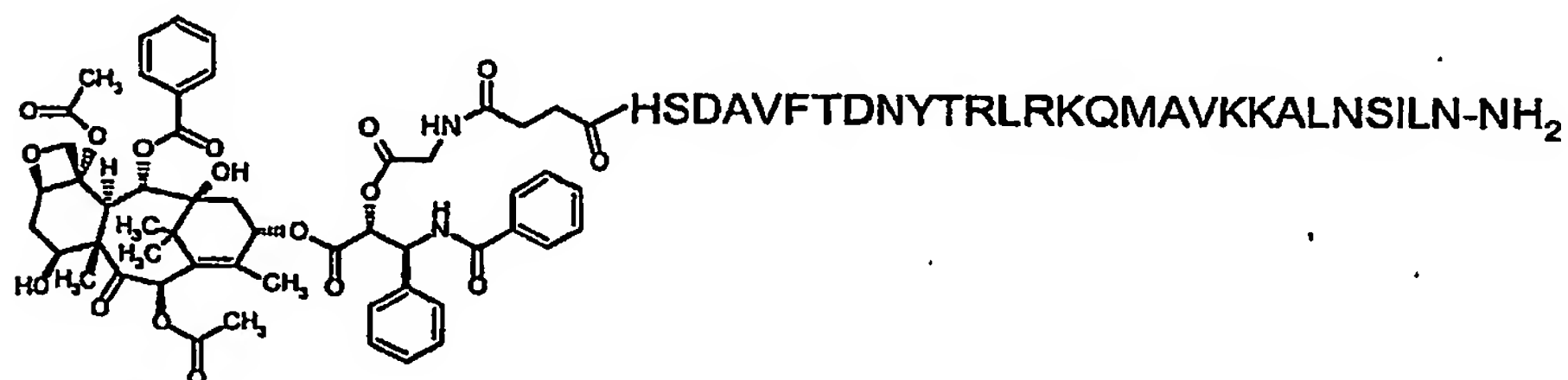
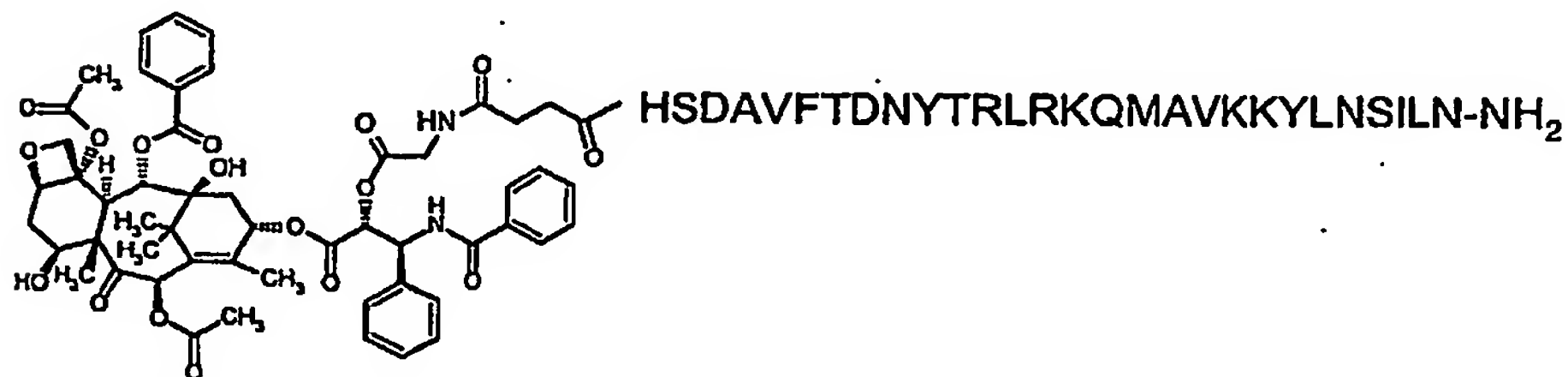
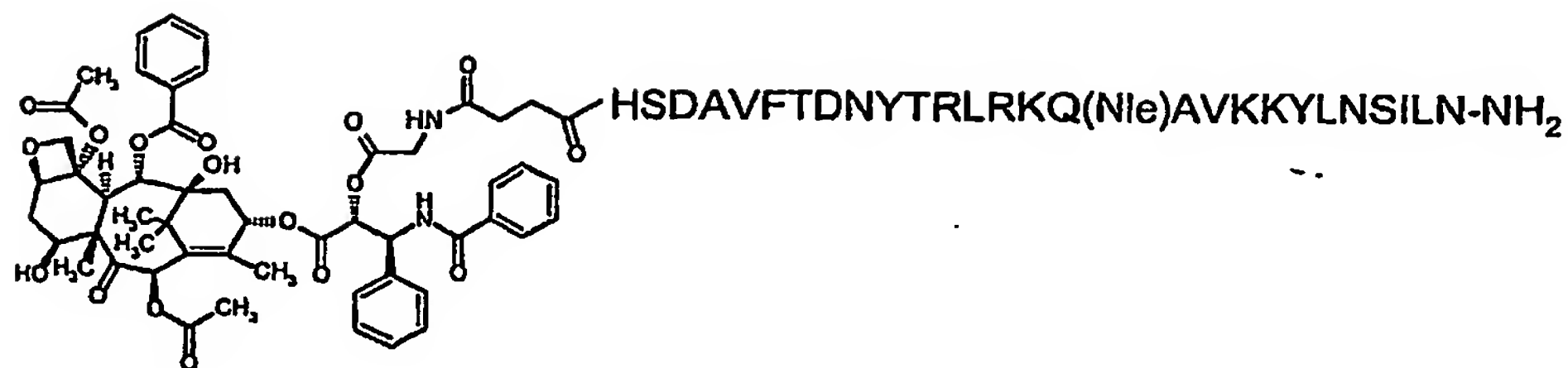




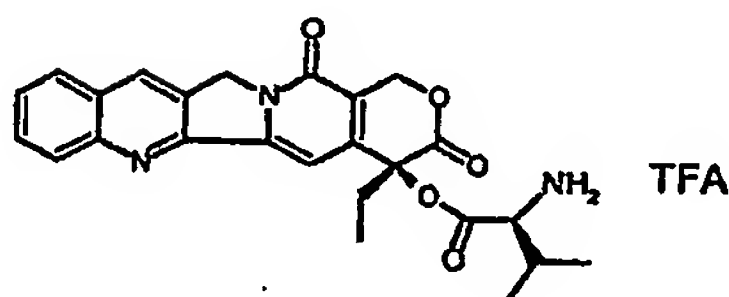
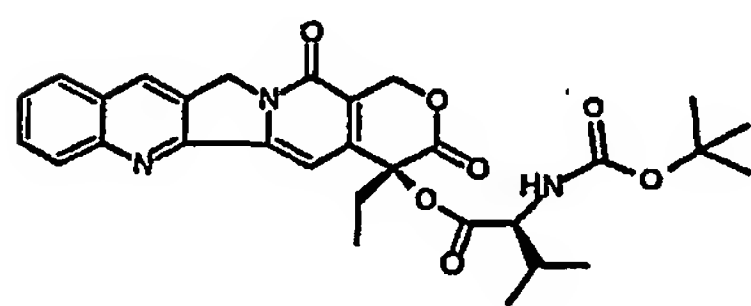
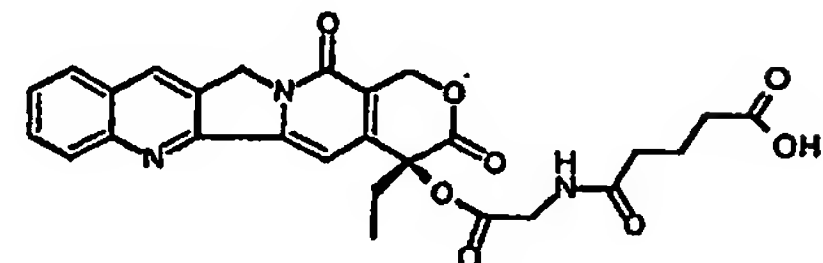
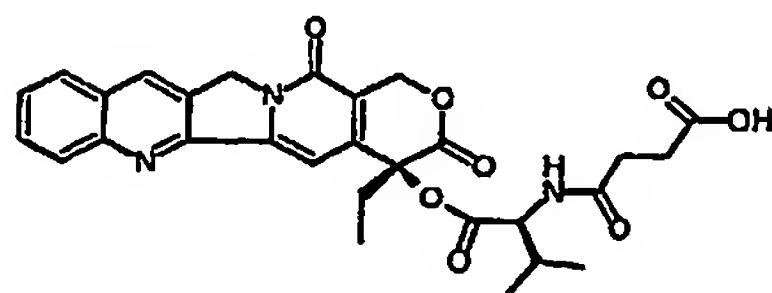
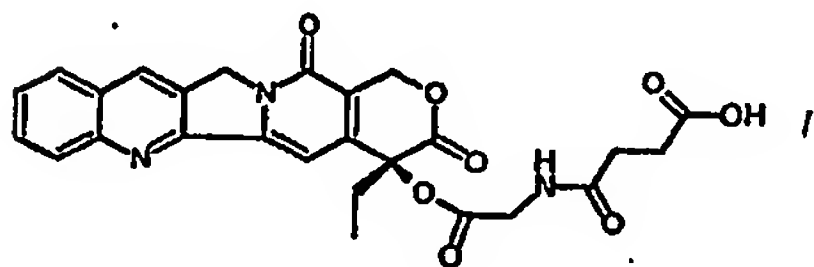
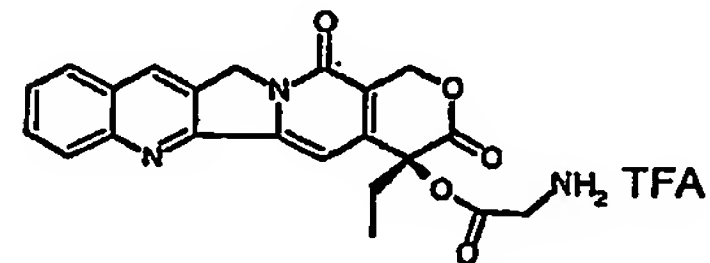
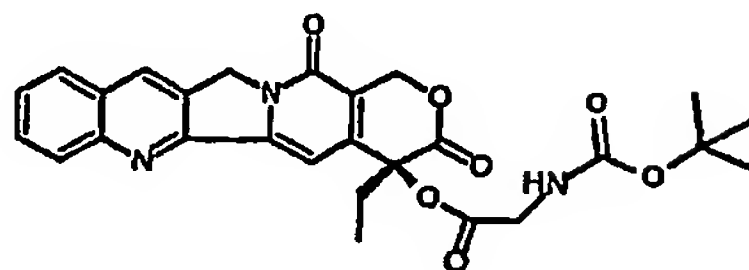
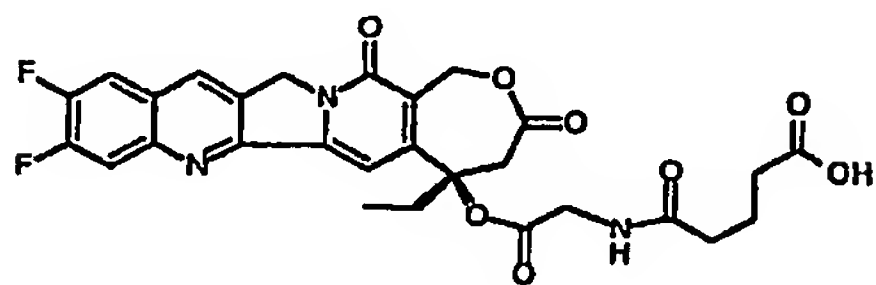
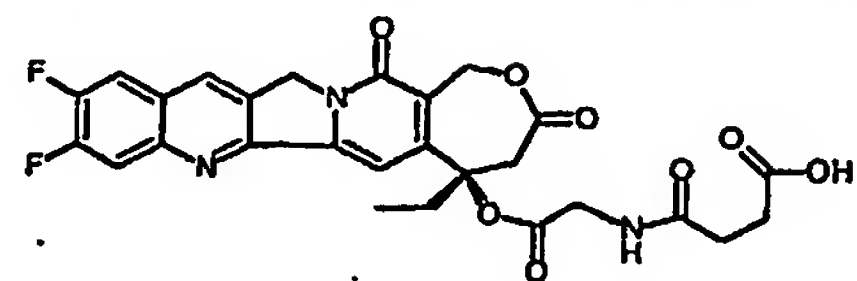
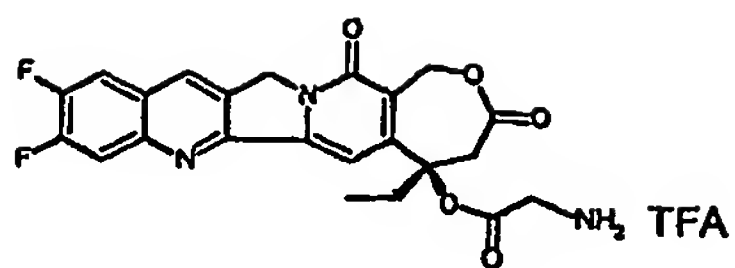
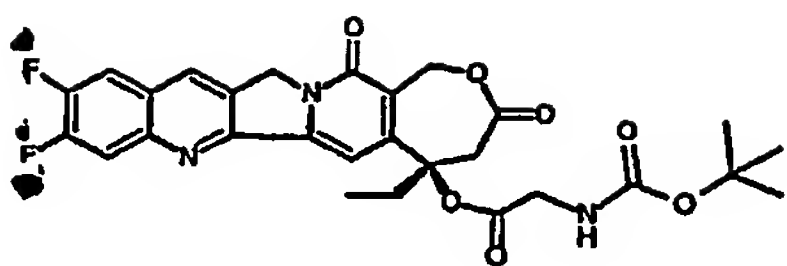




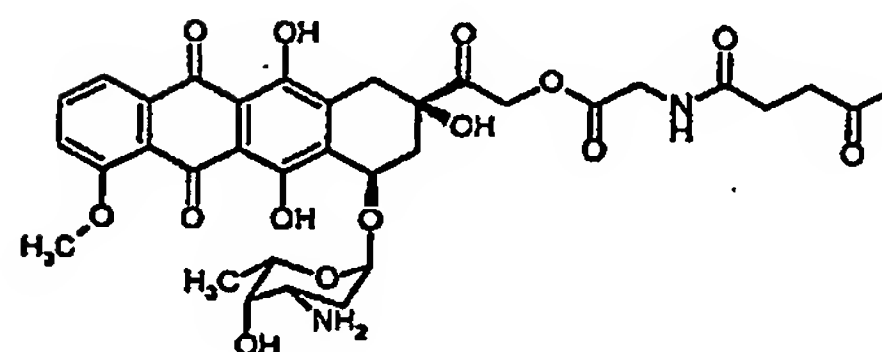
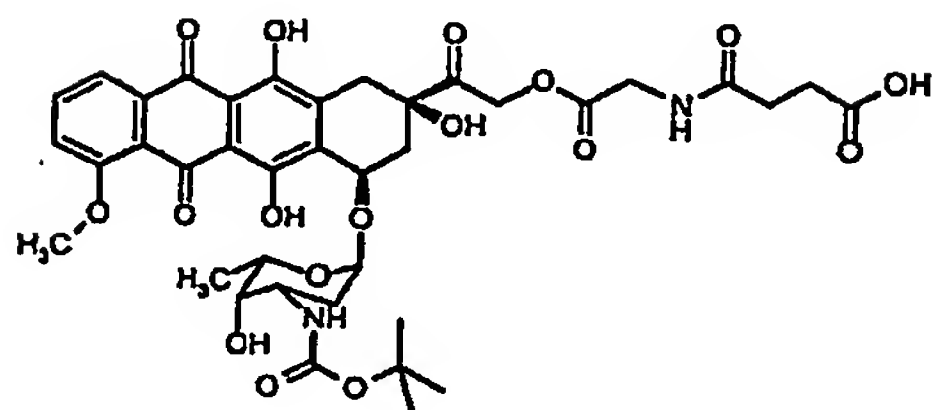
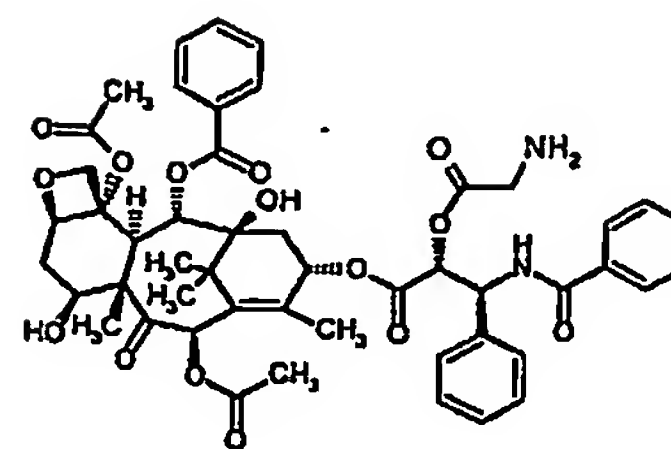
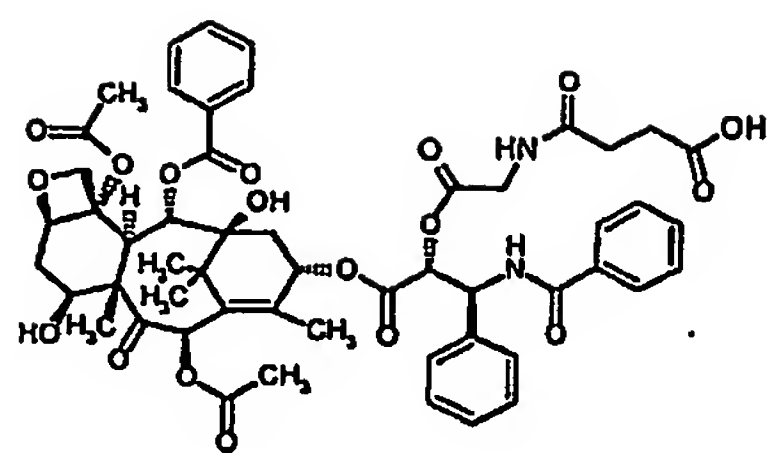




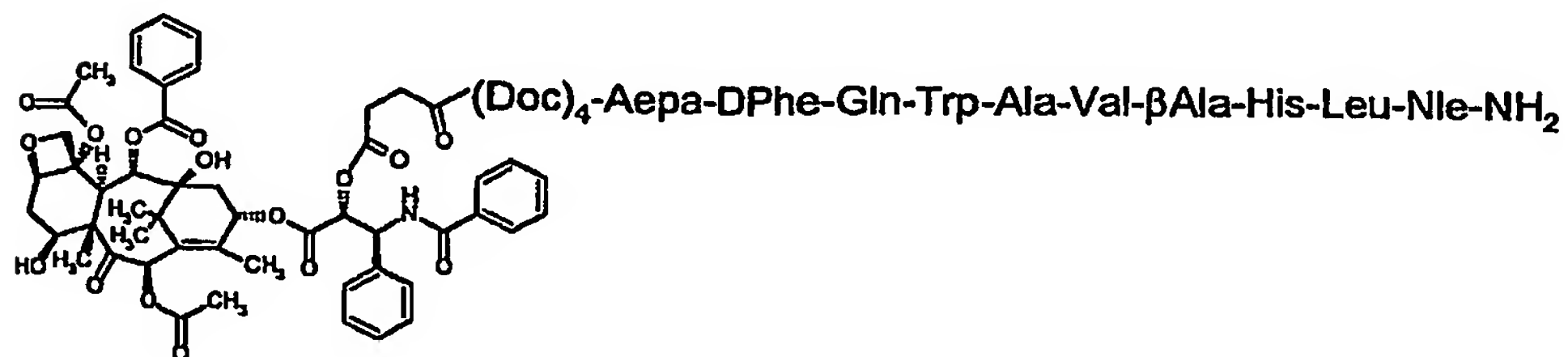
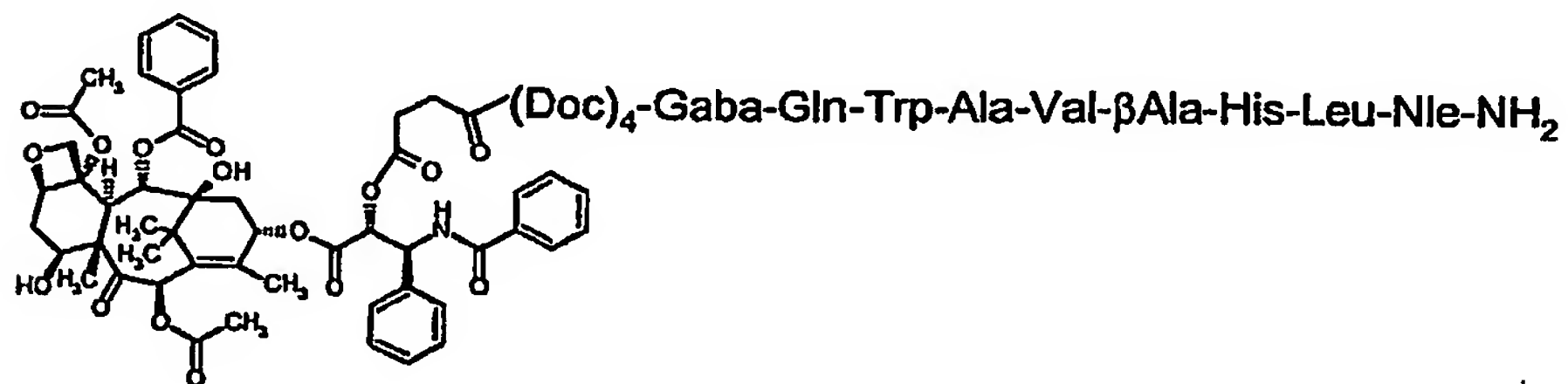
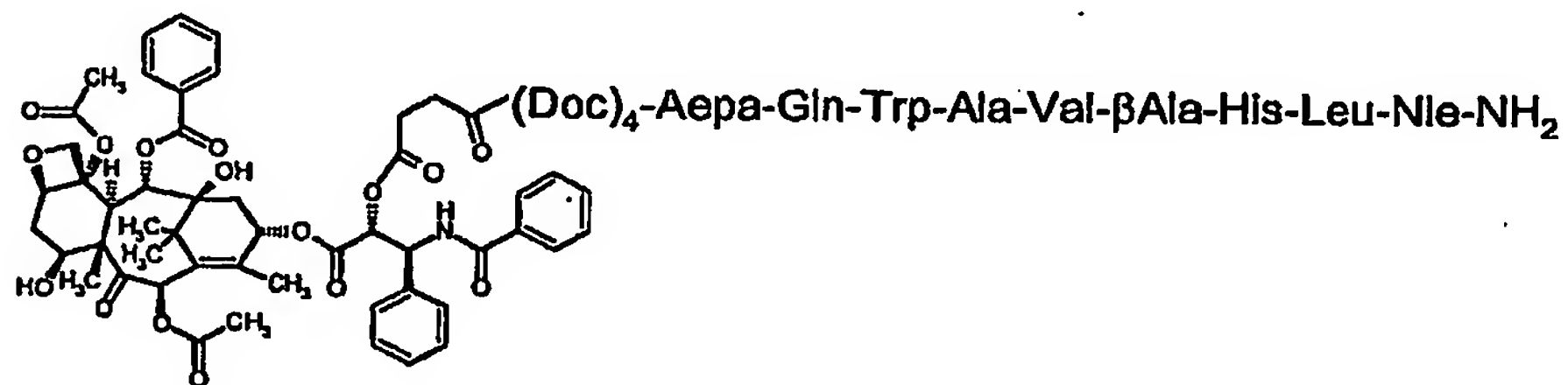
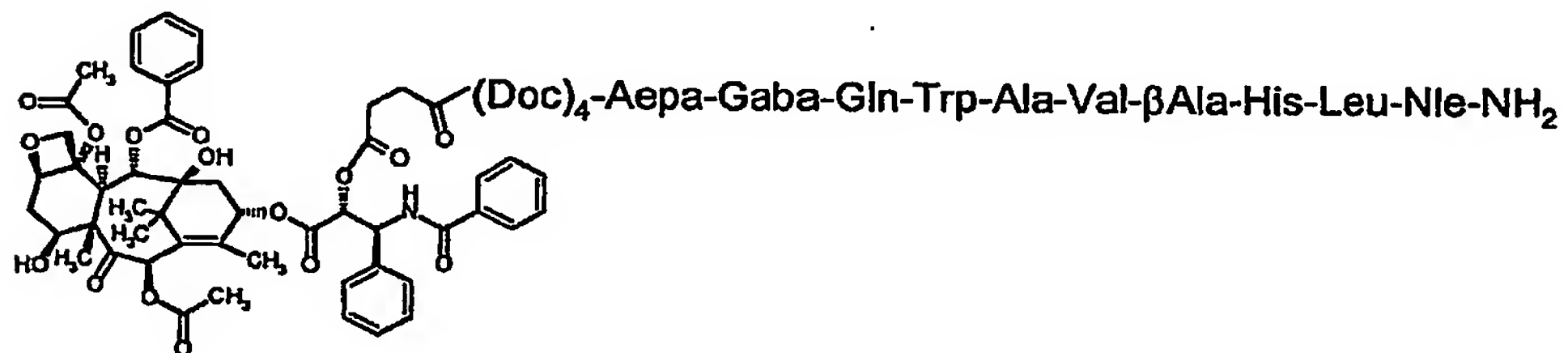
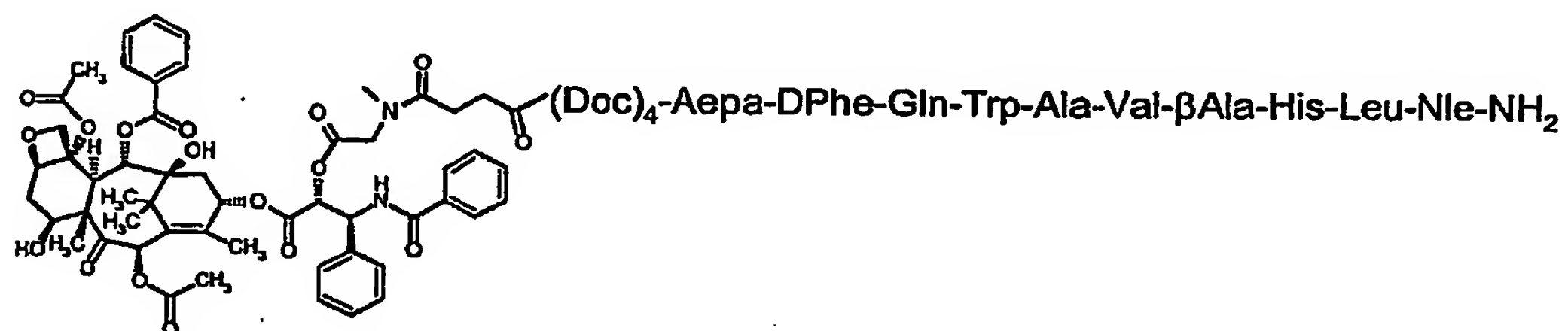
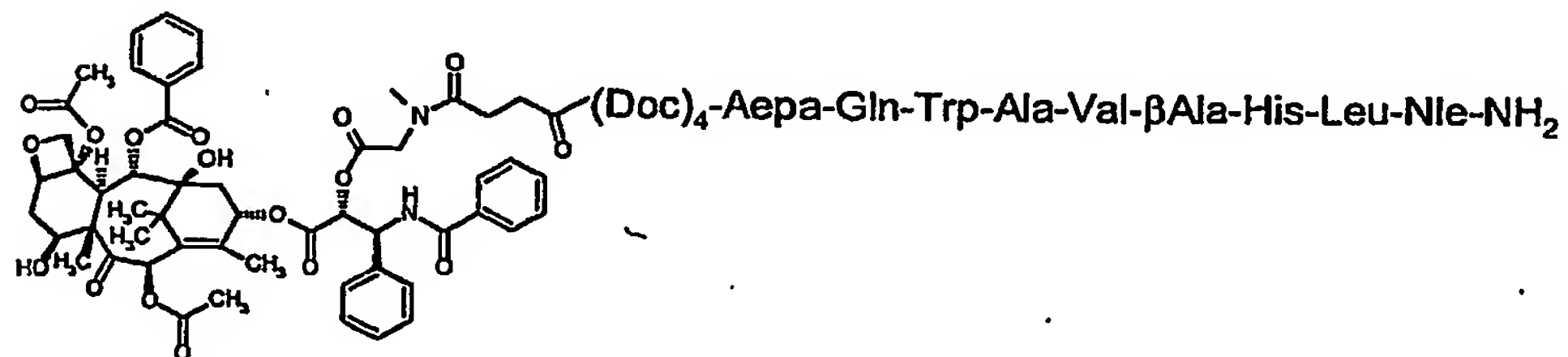
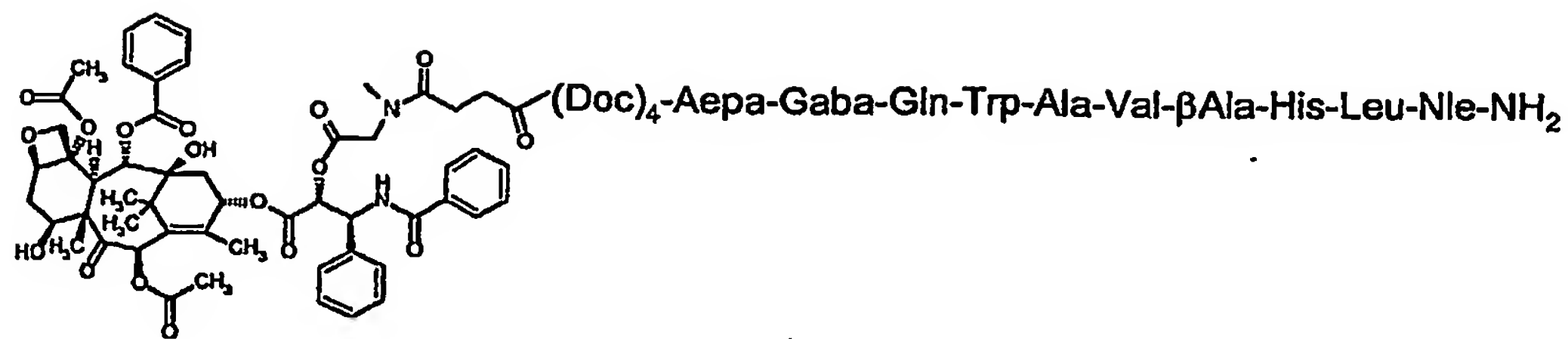
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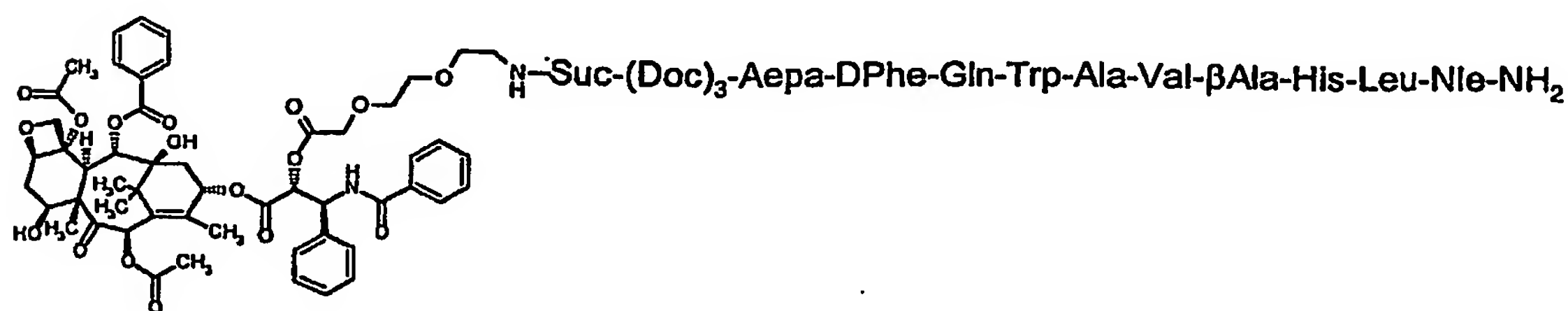
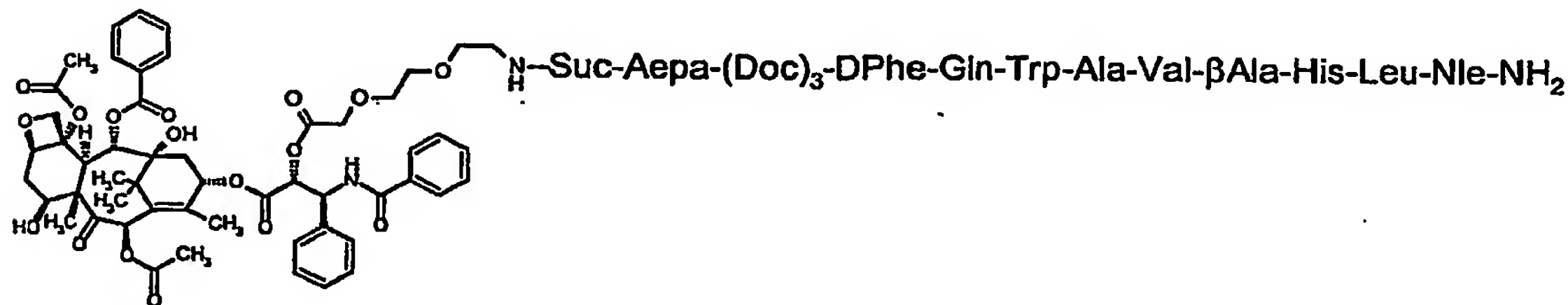
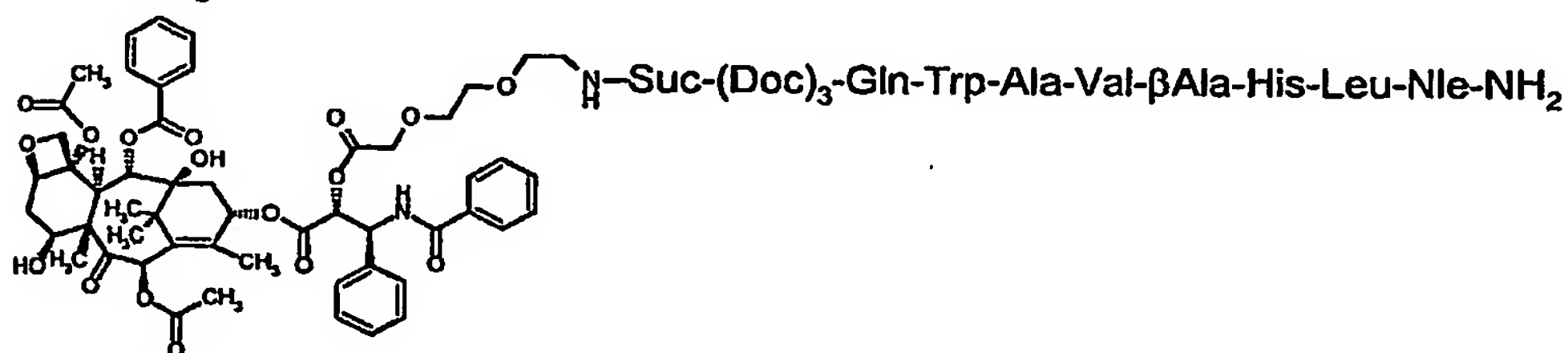
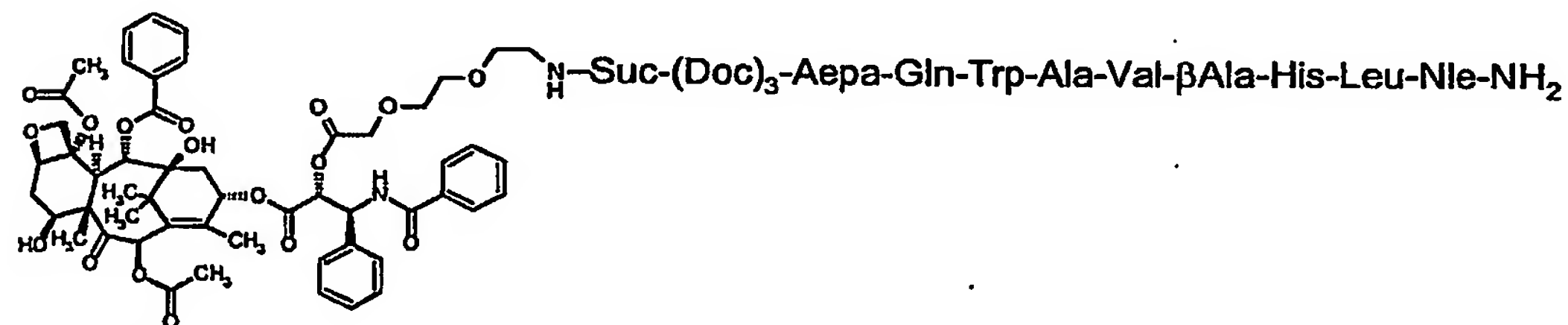
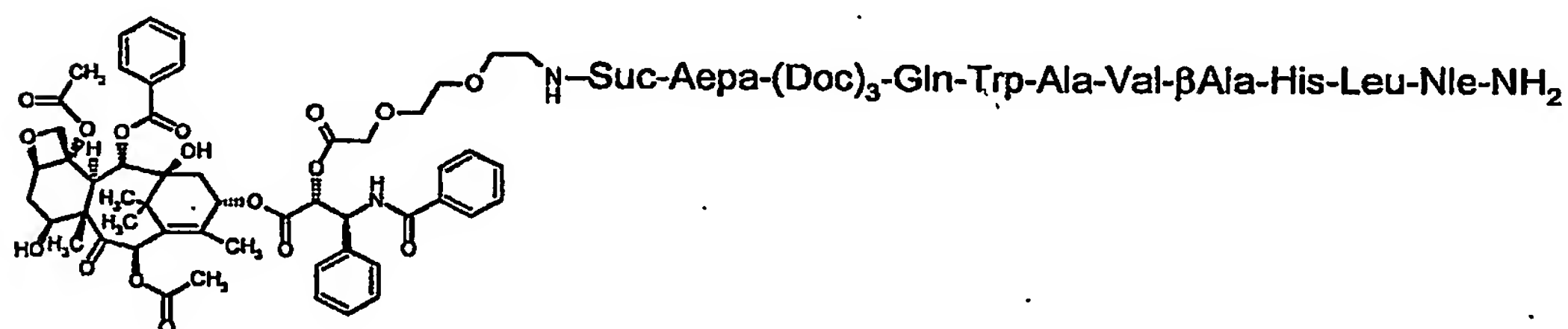
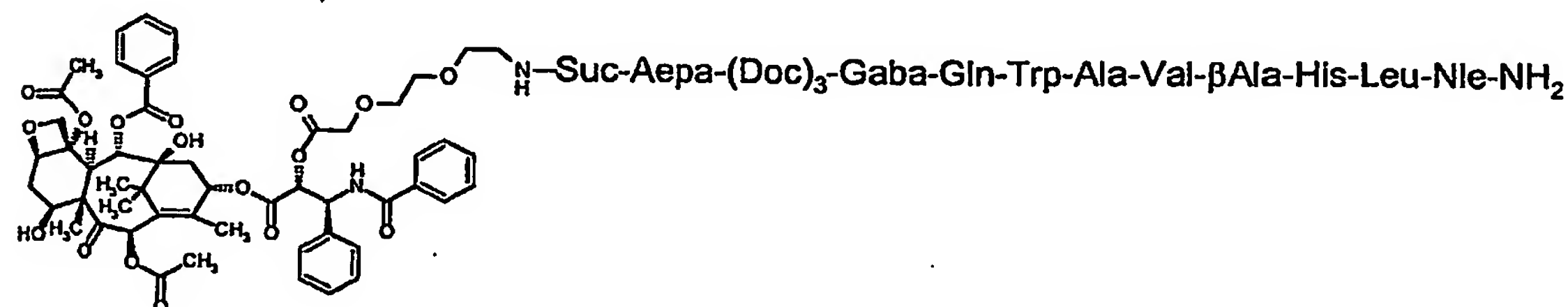
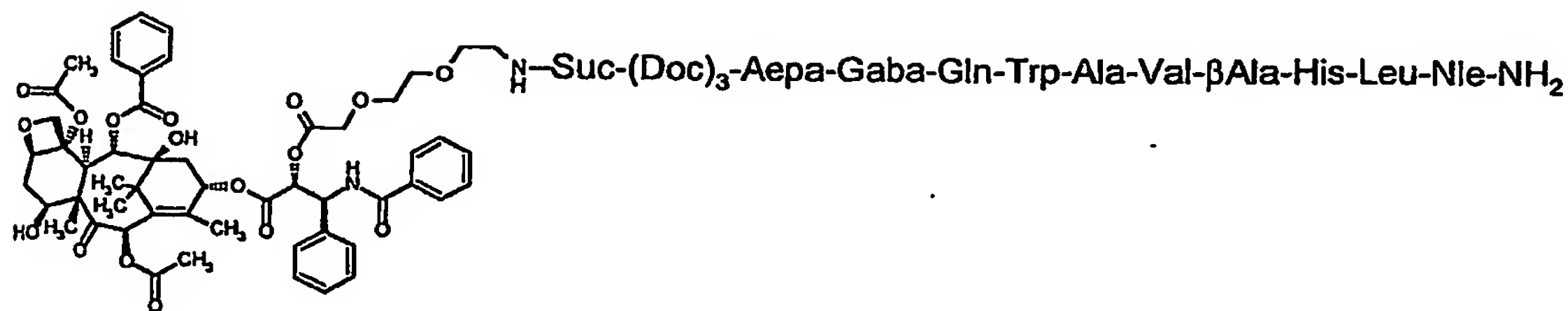


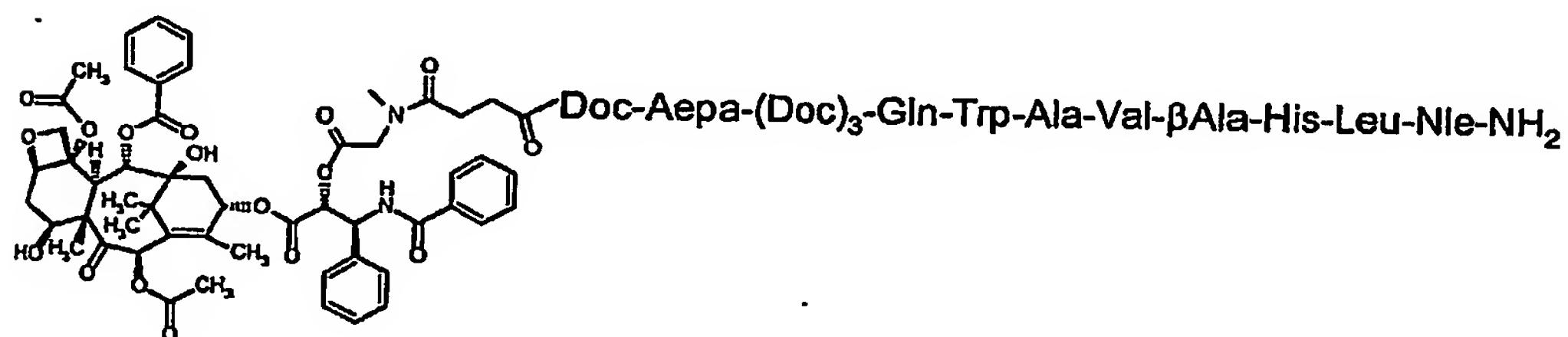
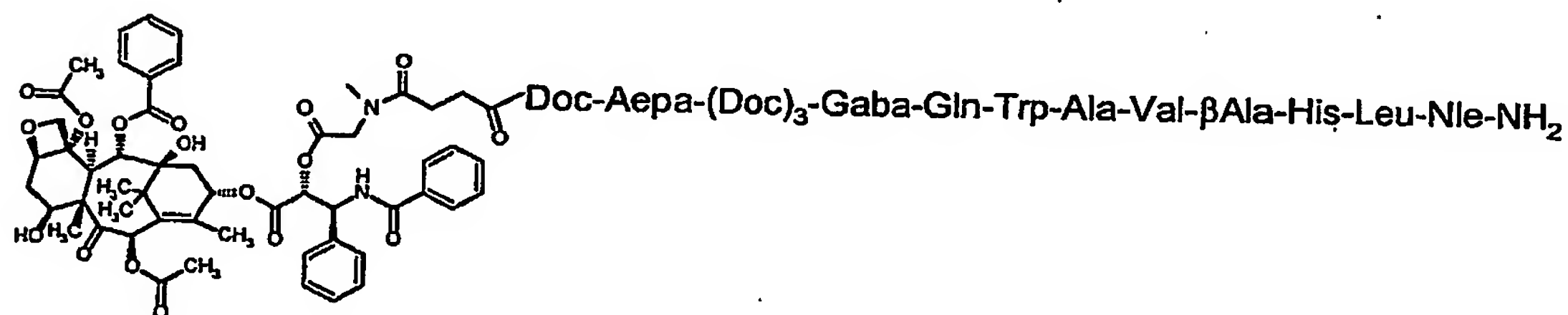
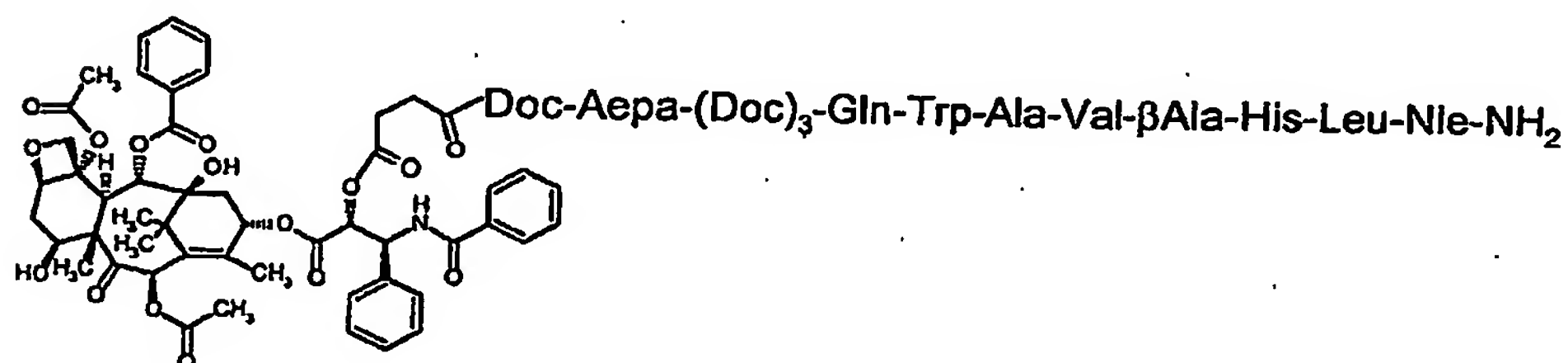
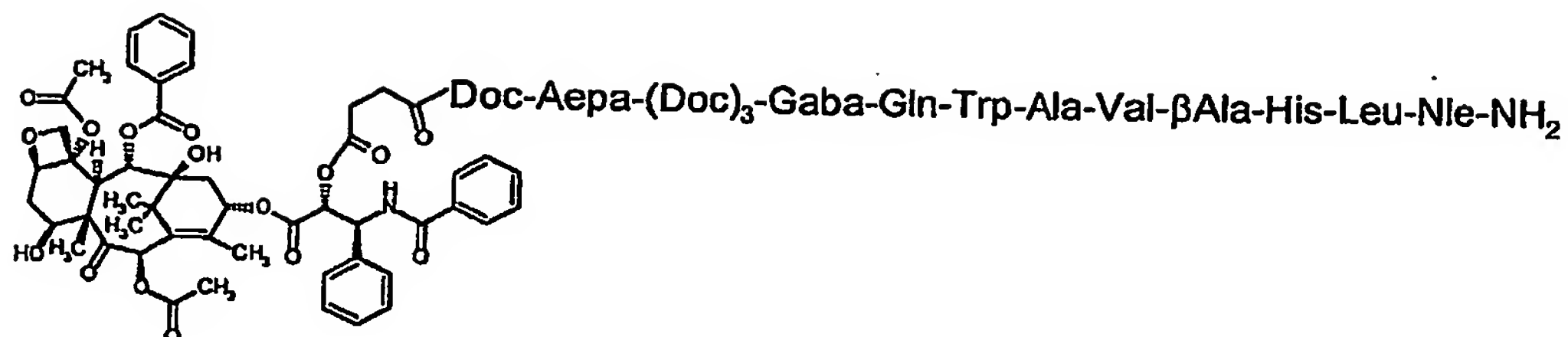
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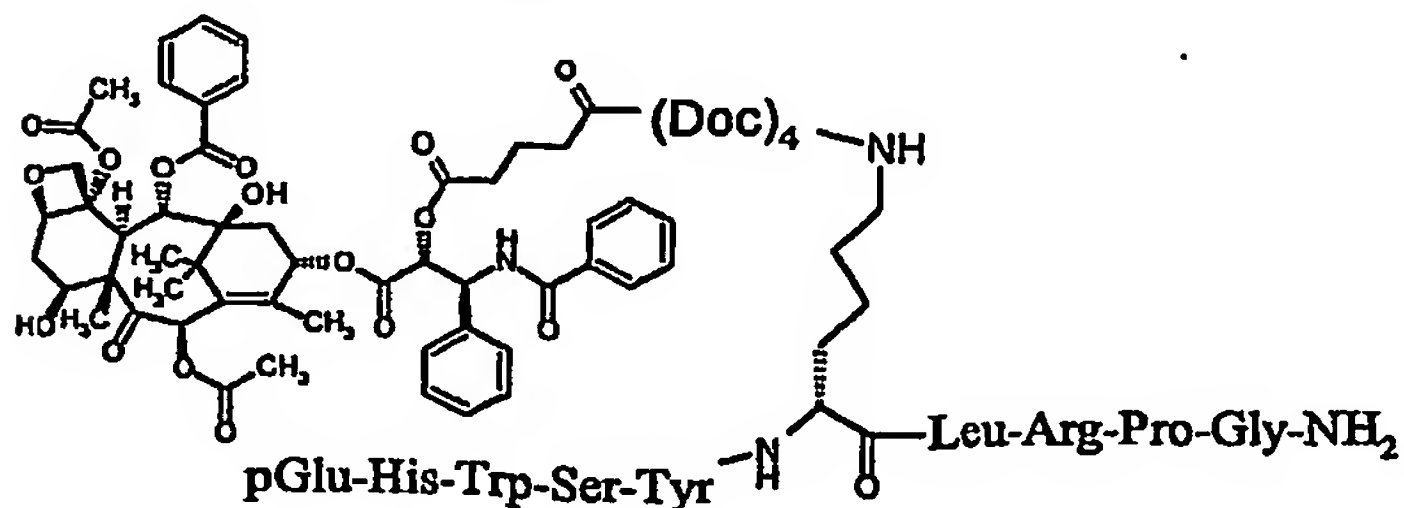
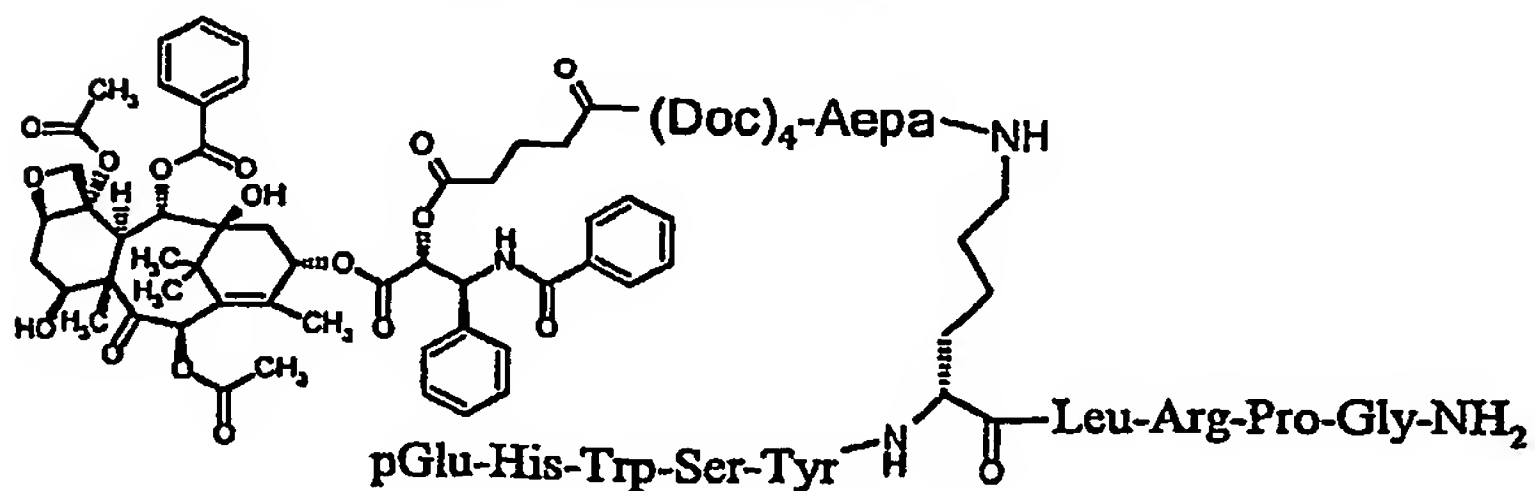
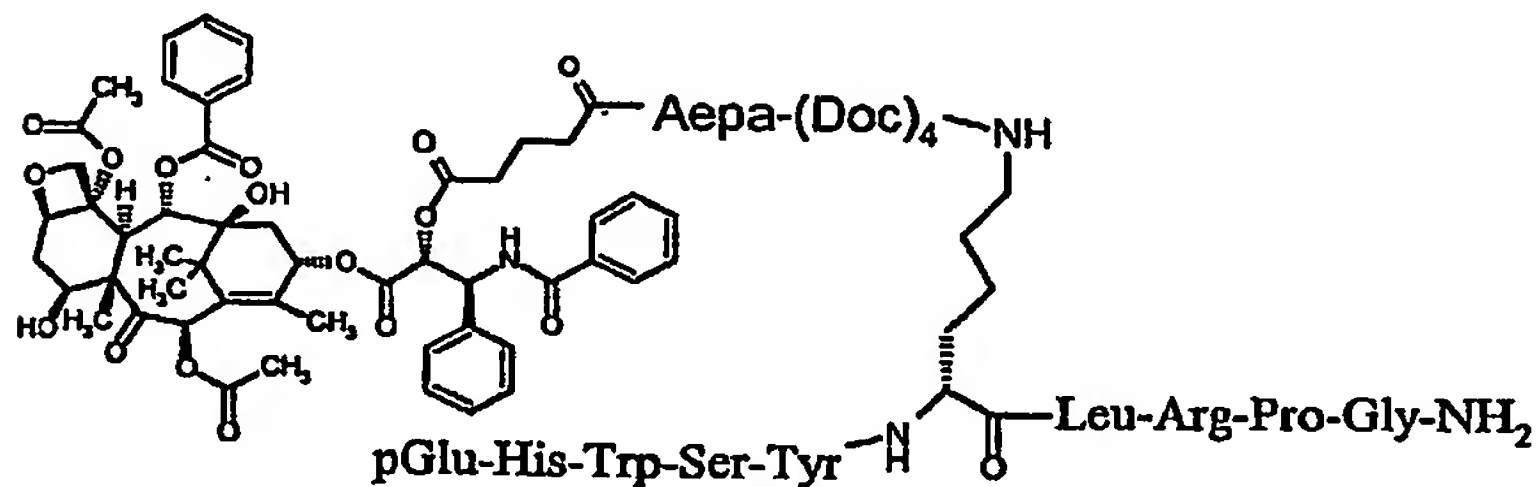
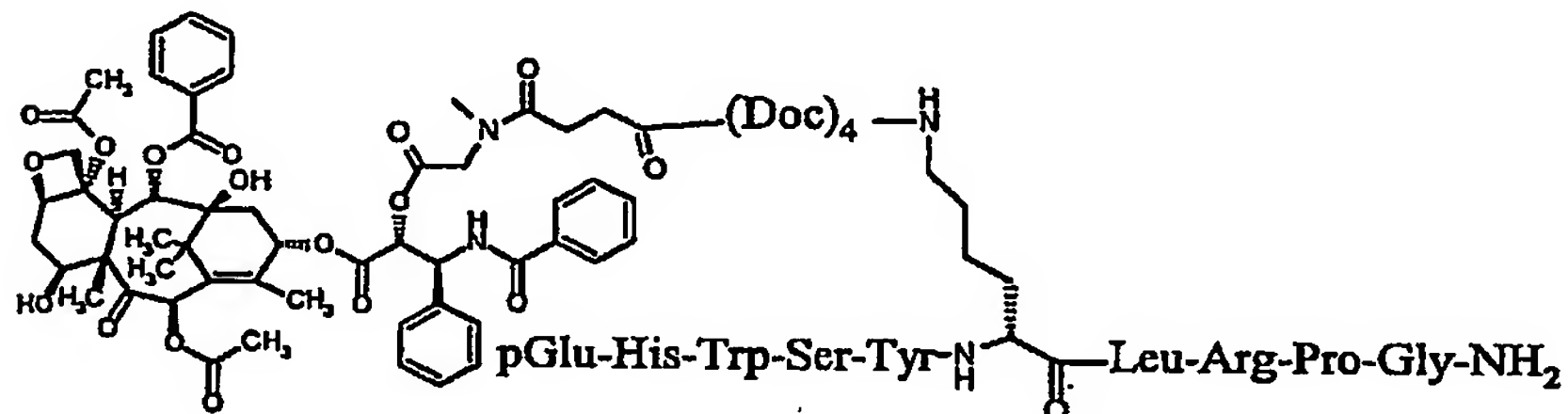
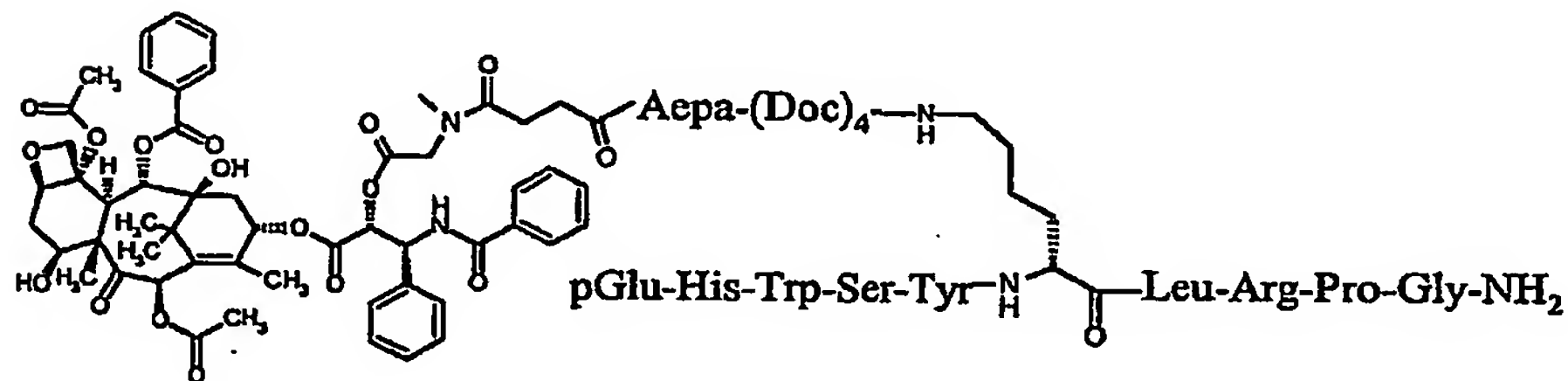
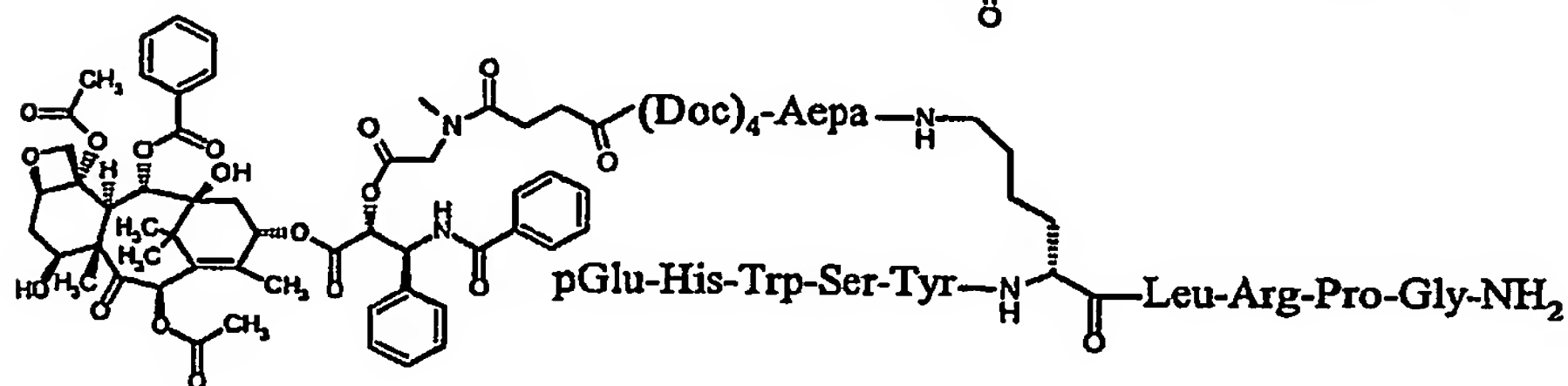
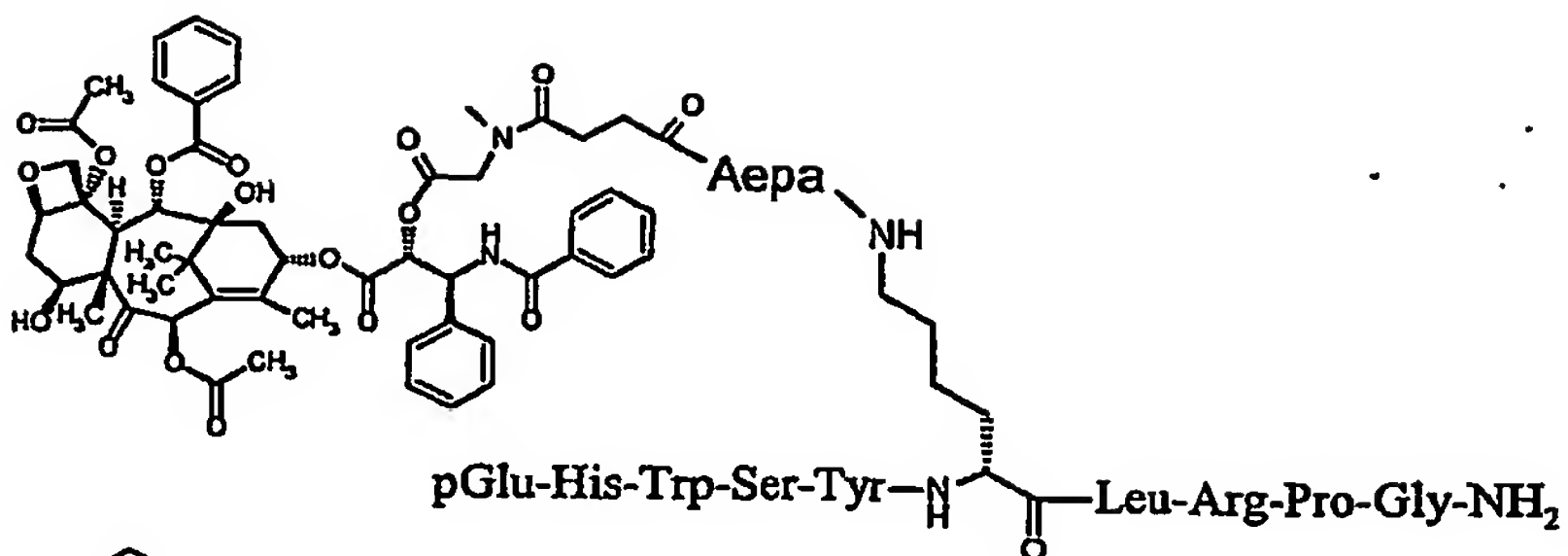


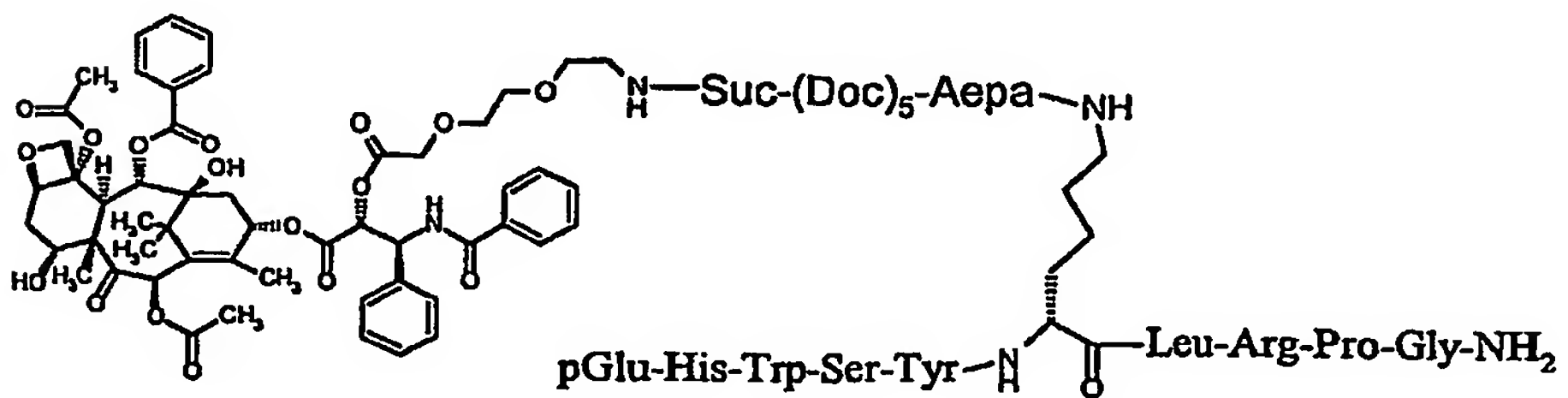
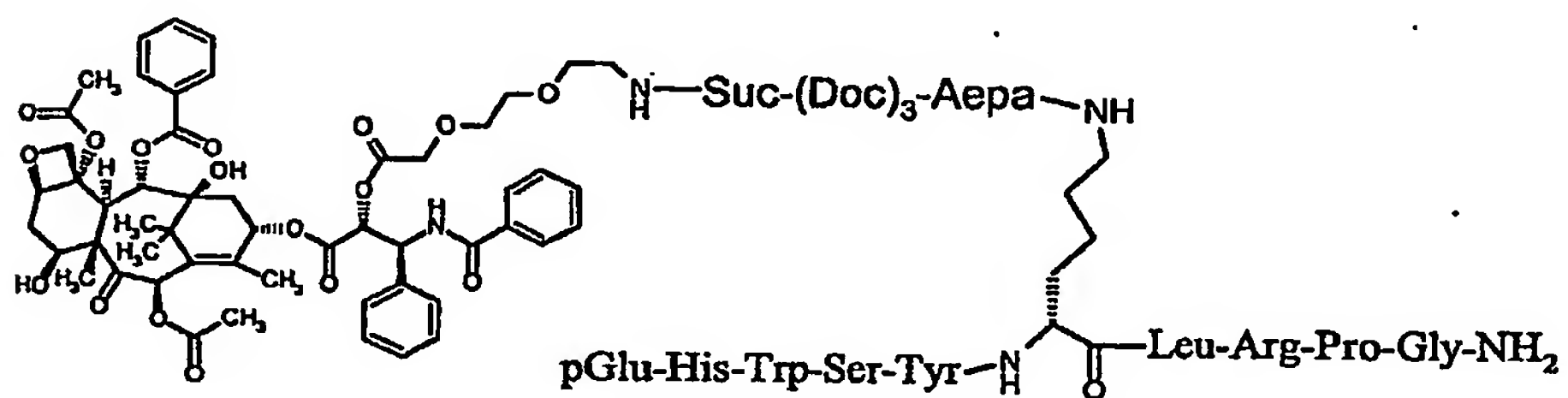
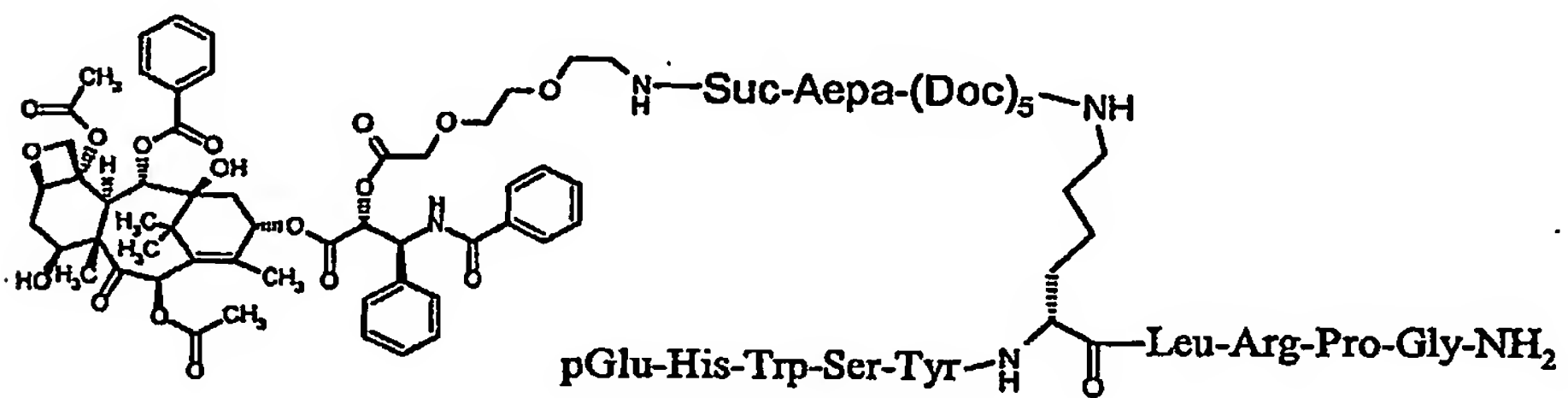
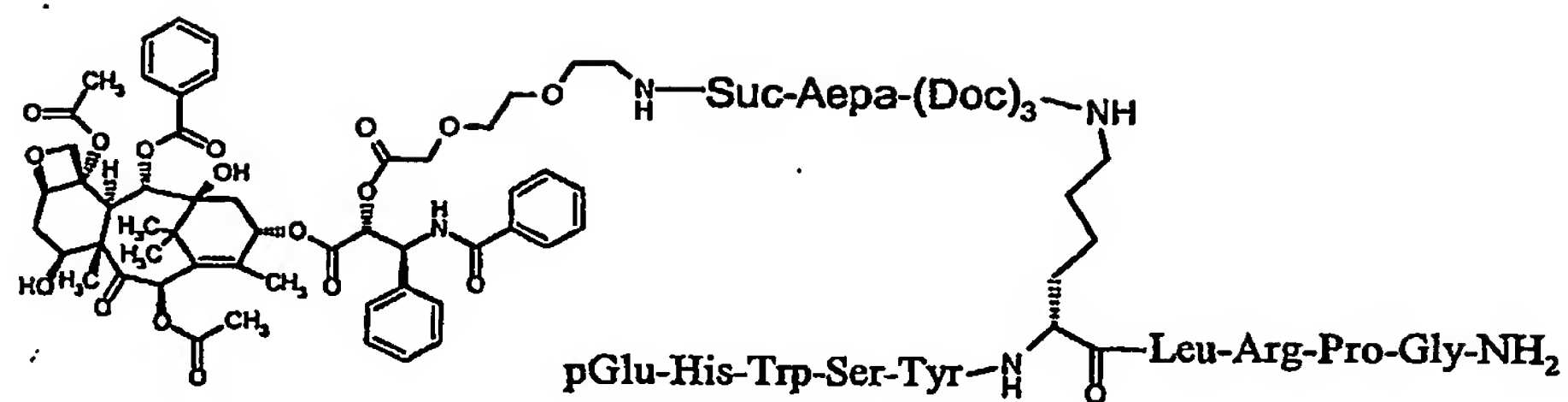
Appendix J

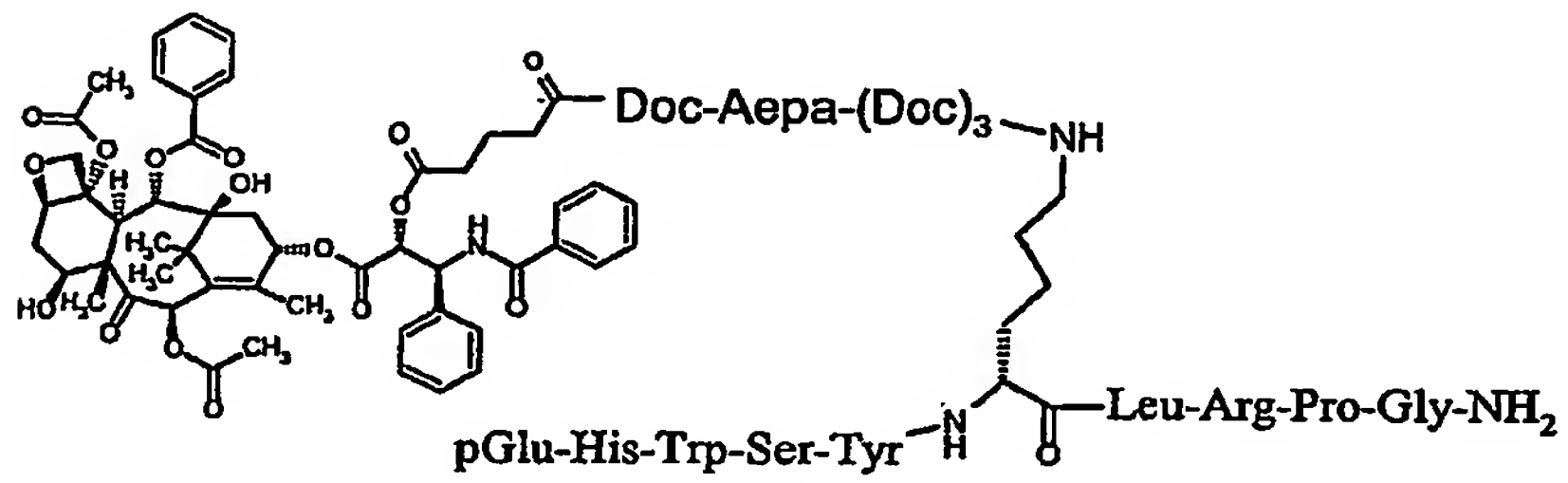
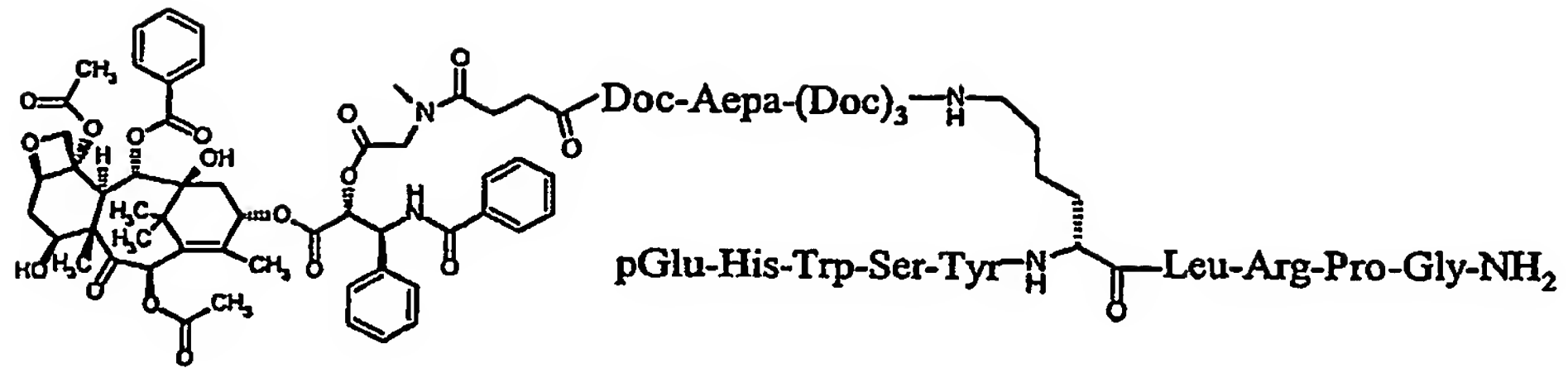


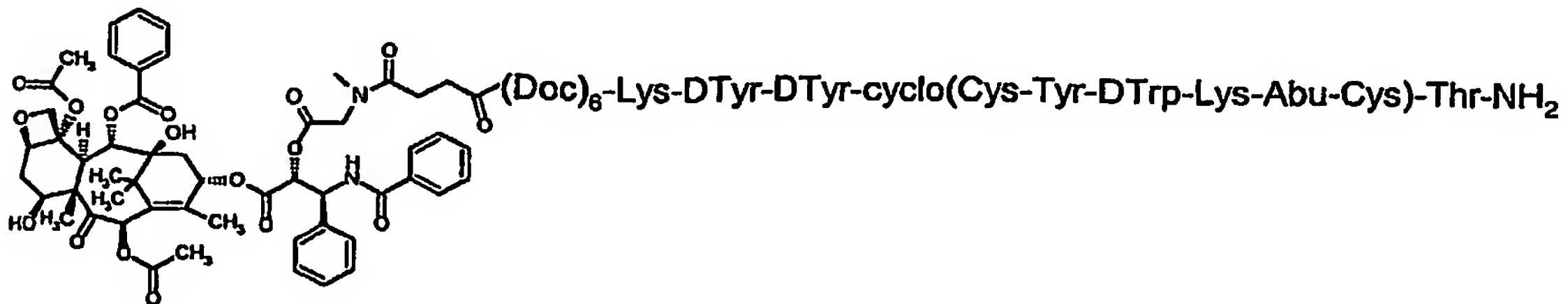
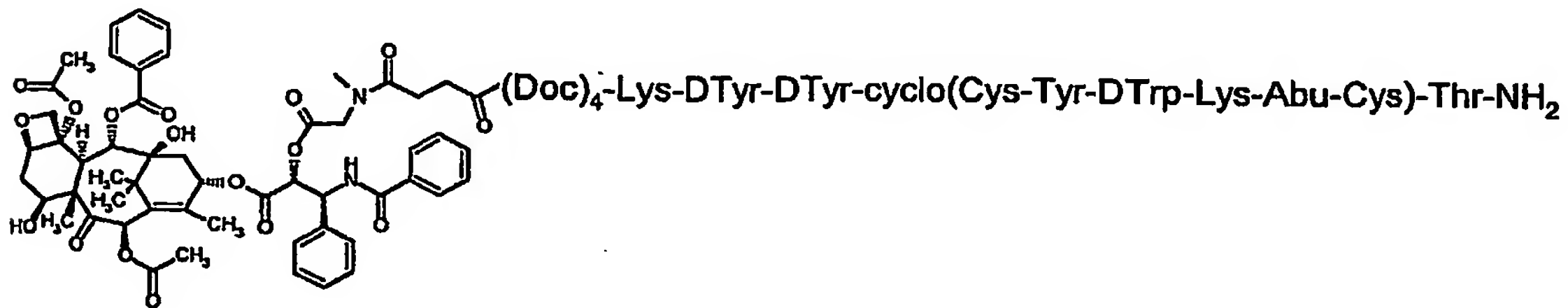
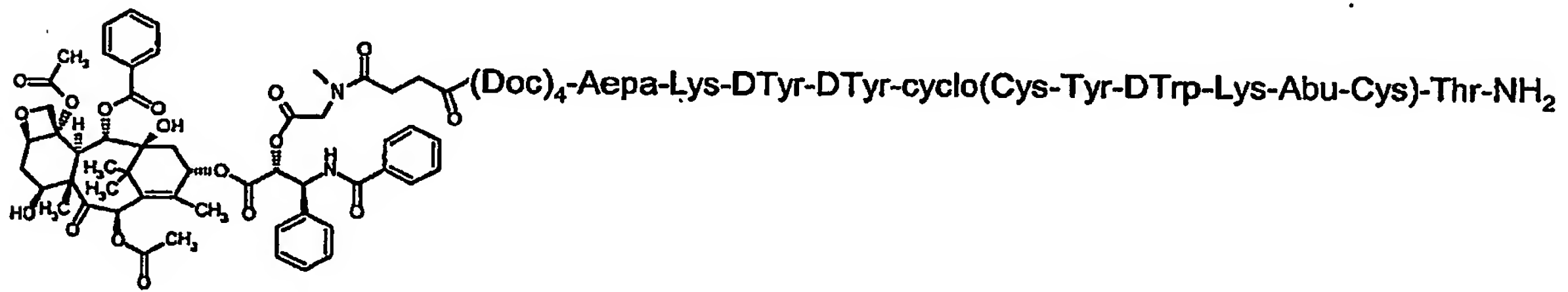
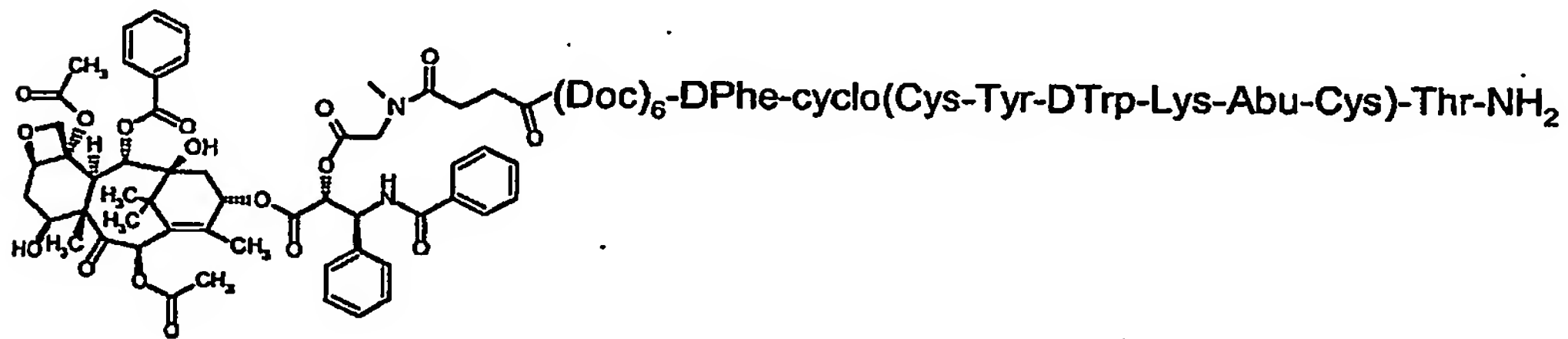
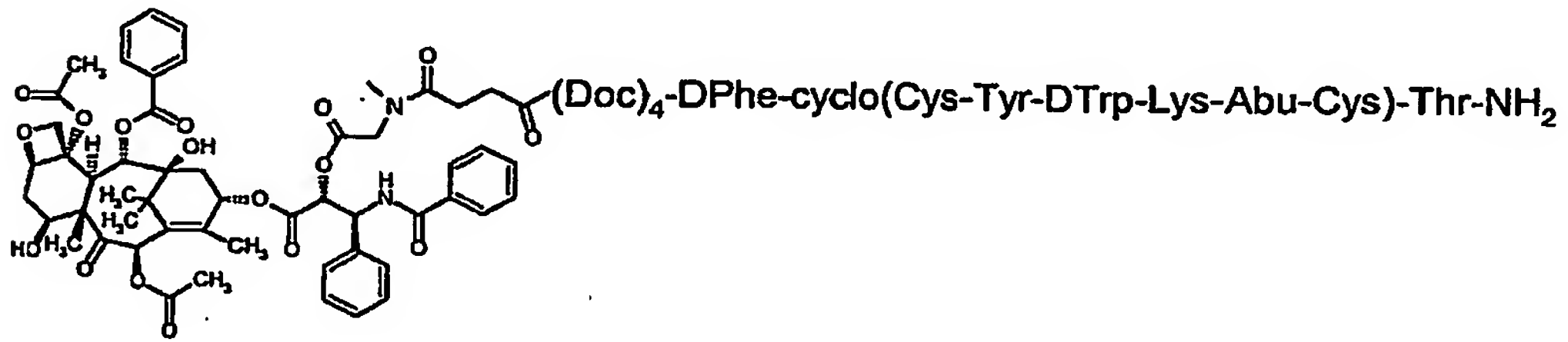
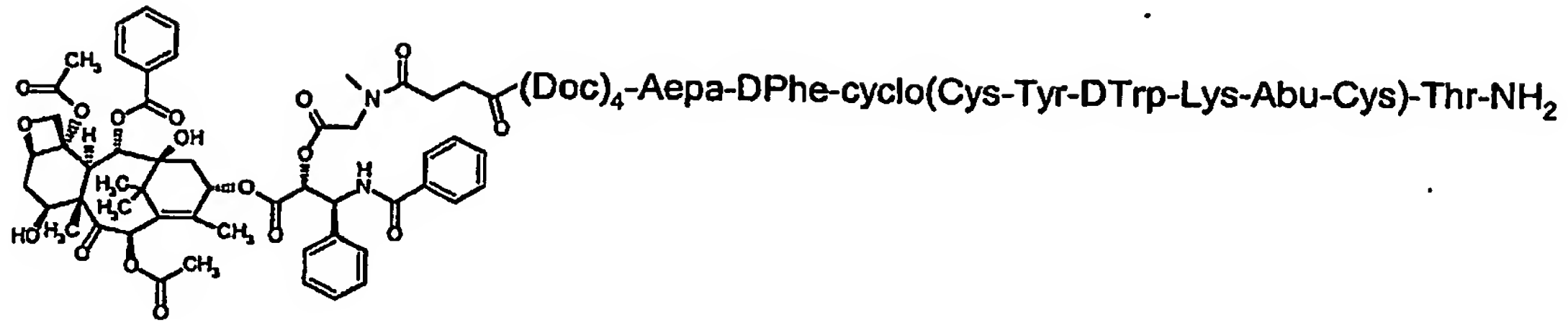


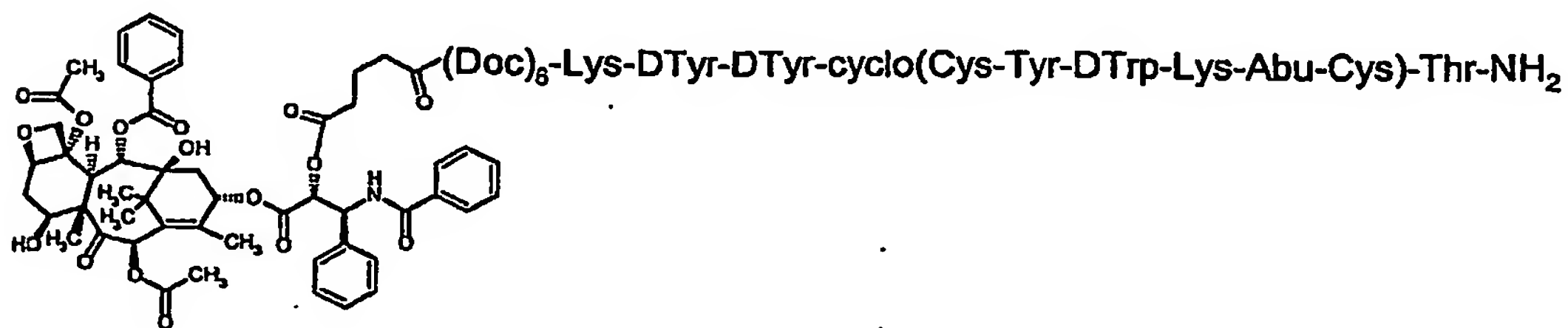
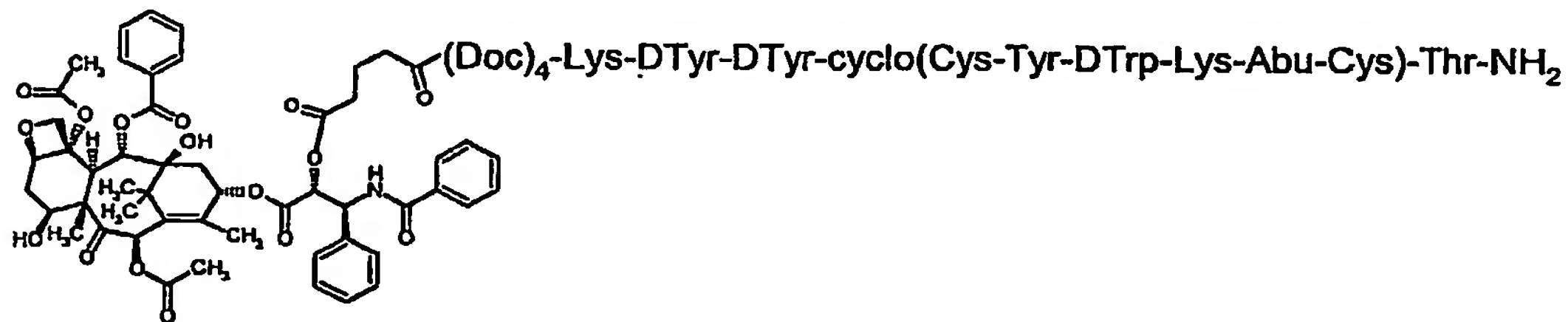
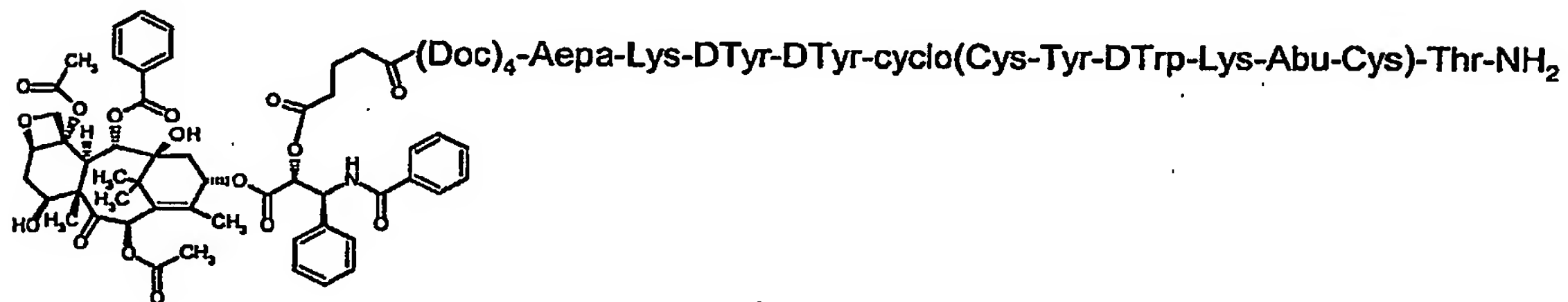
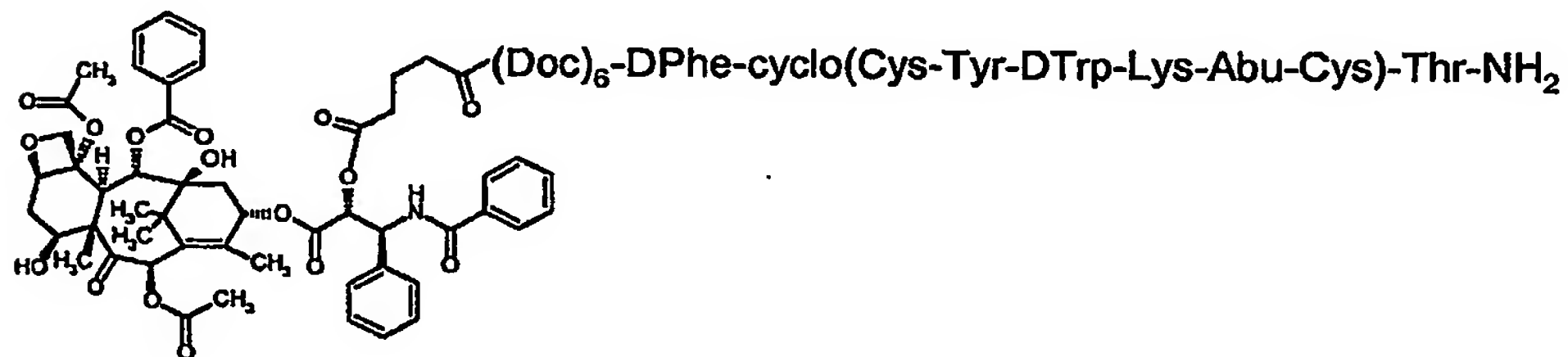
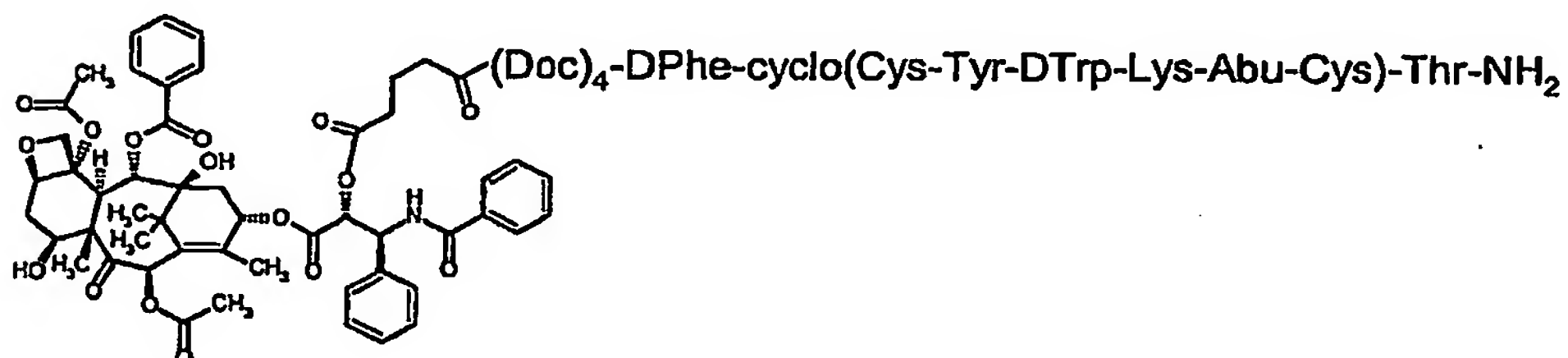
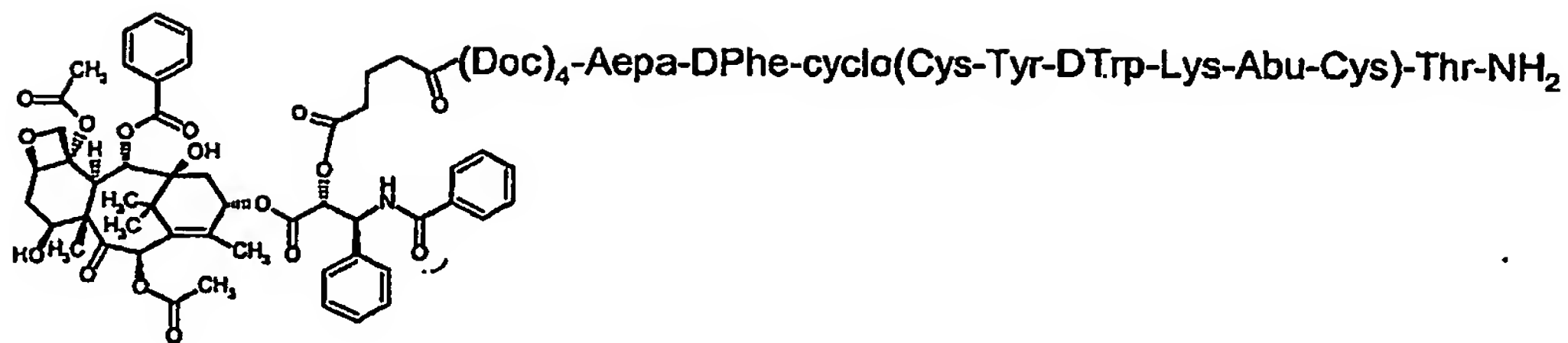




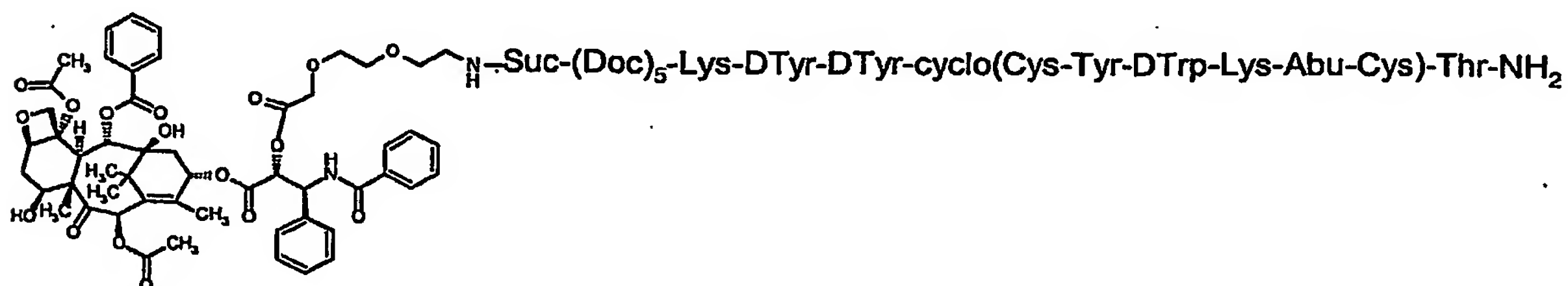
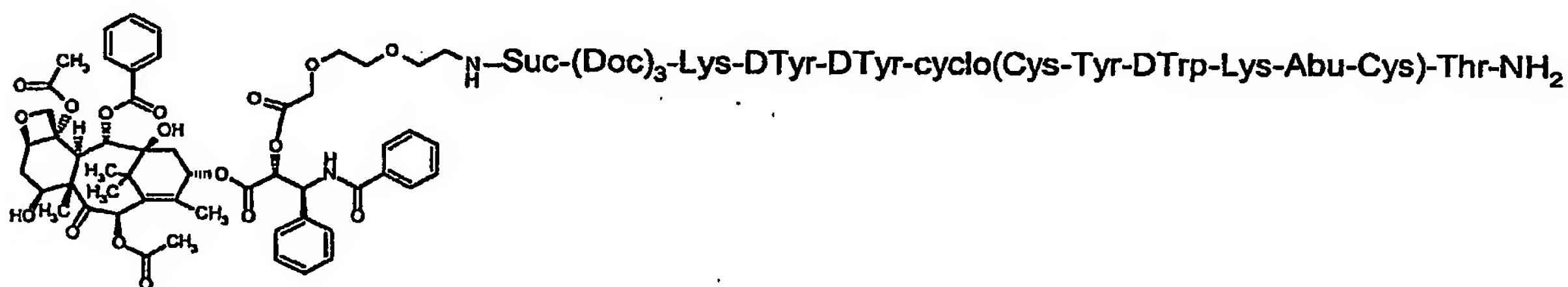
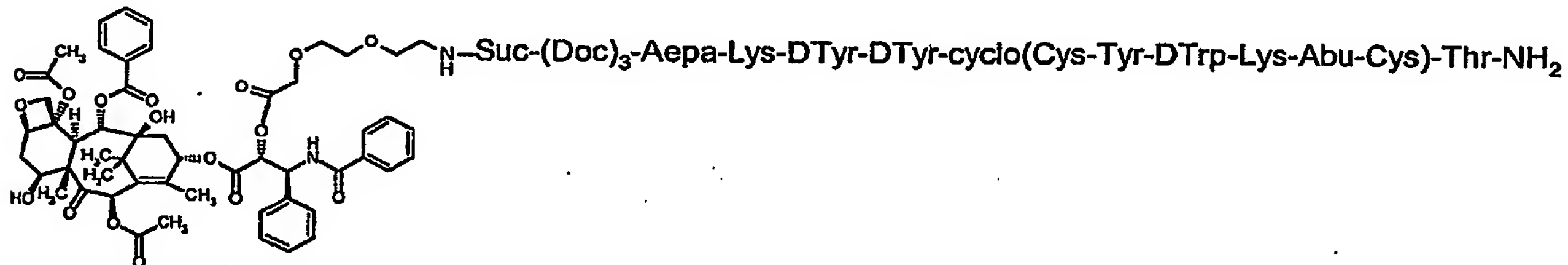
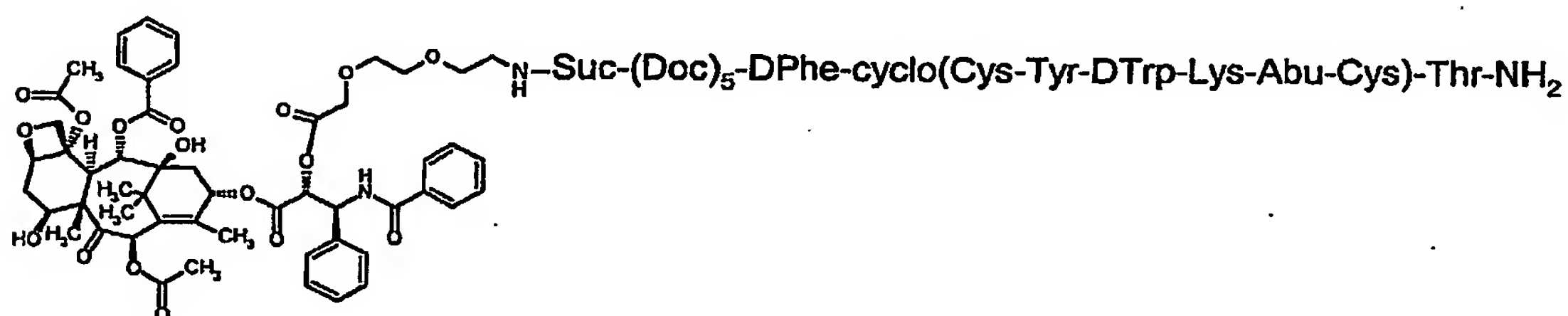
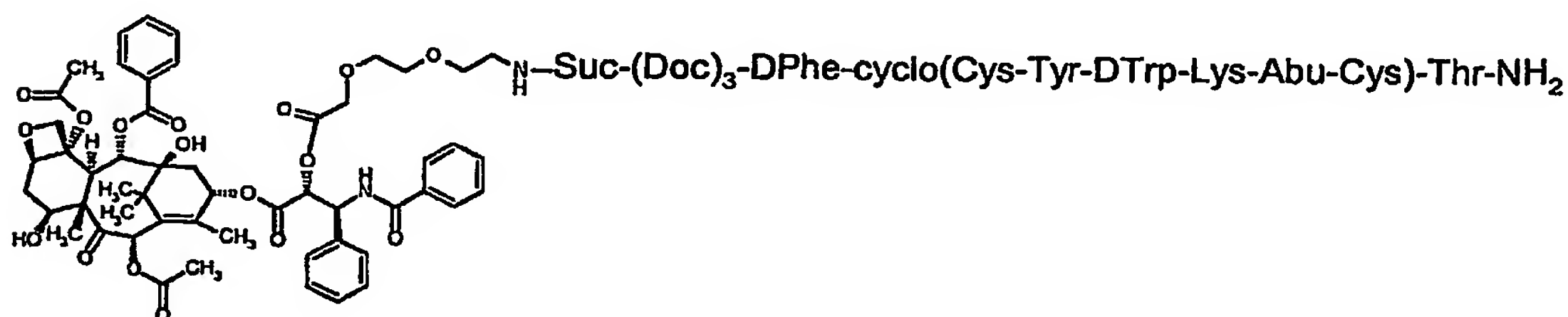
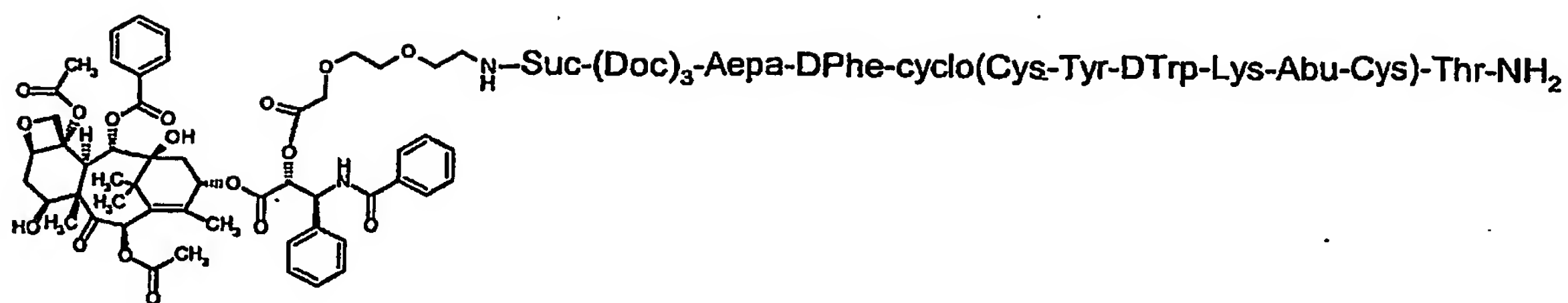


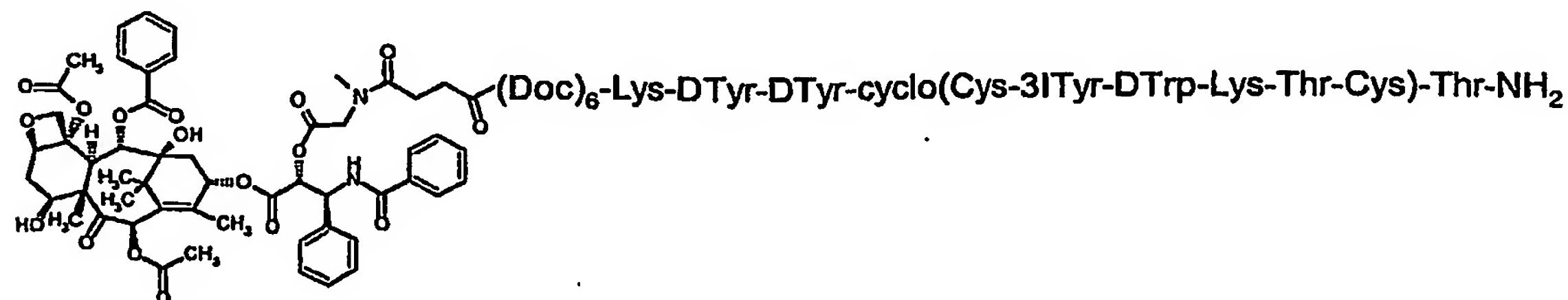
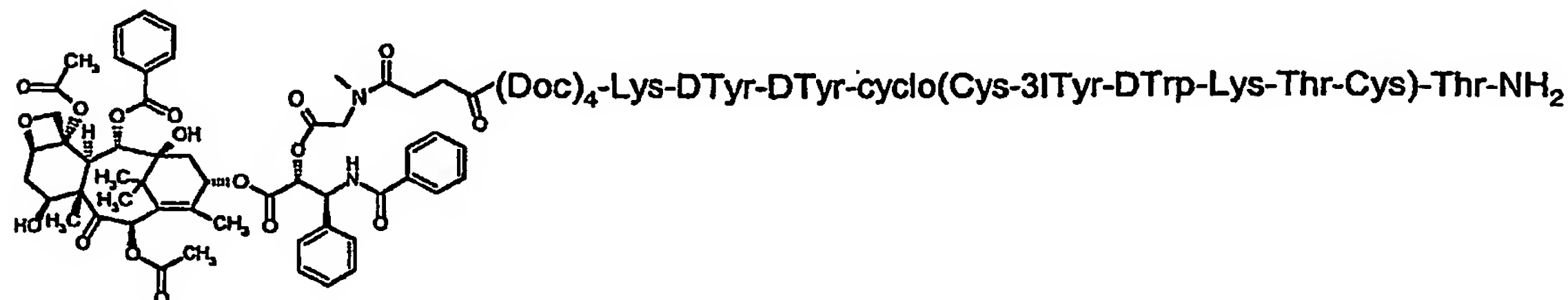
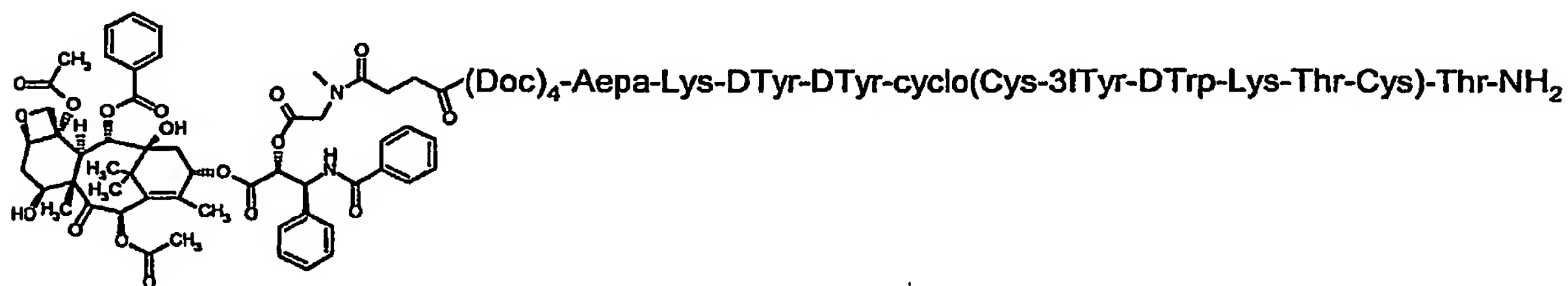
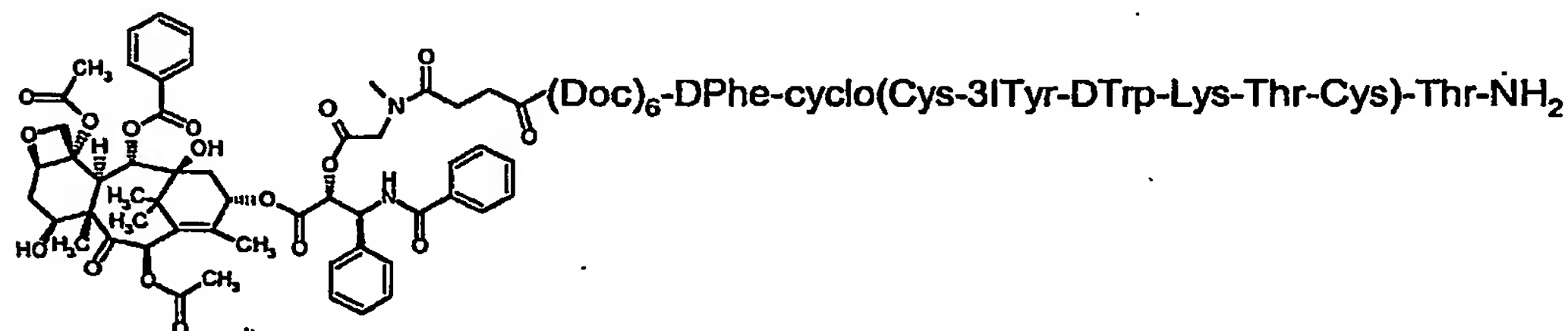
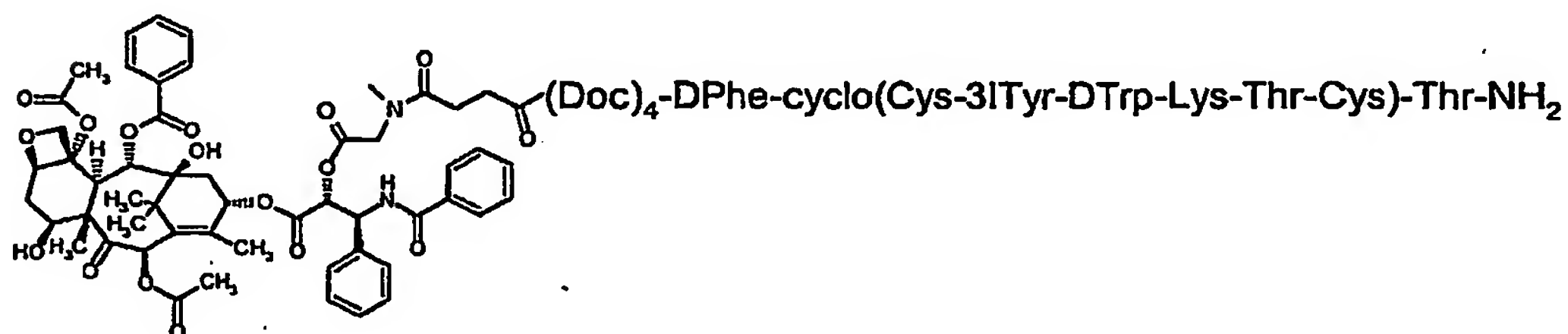
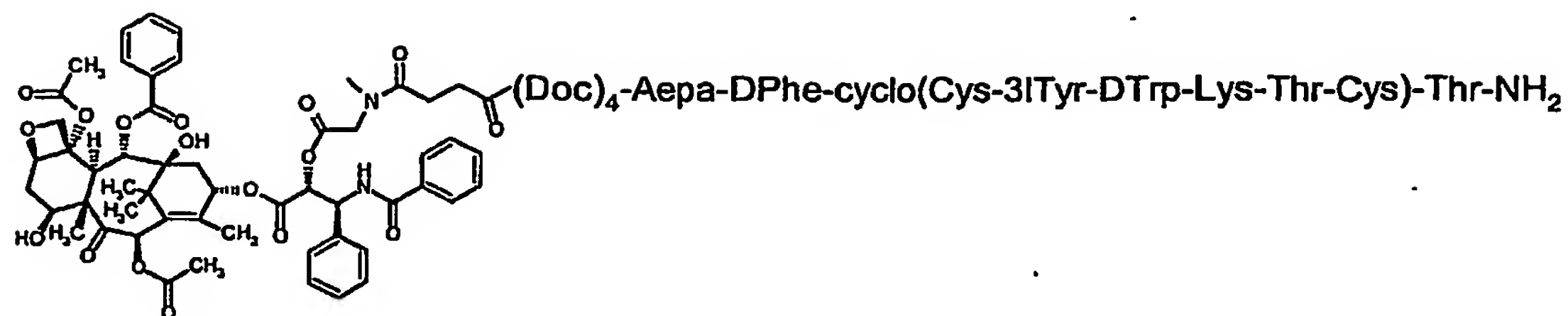


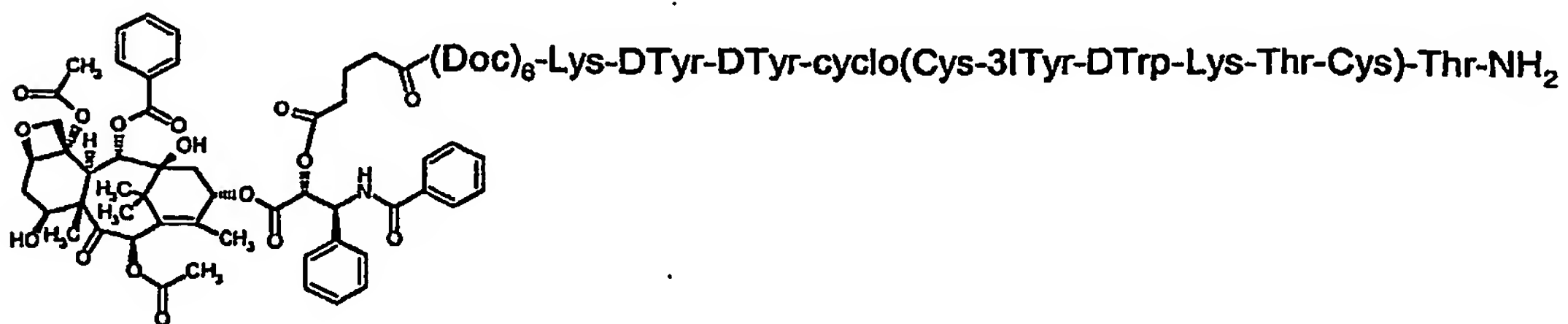
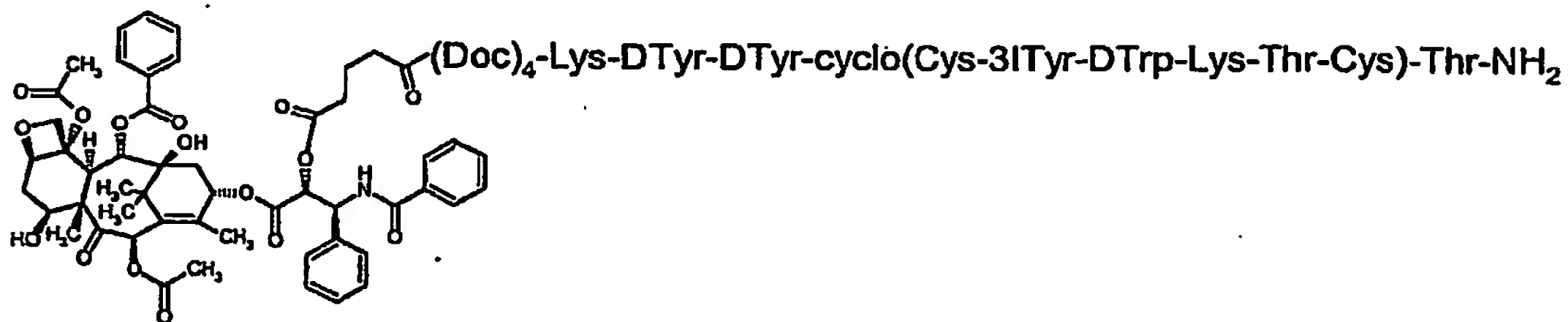
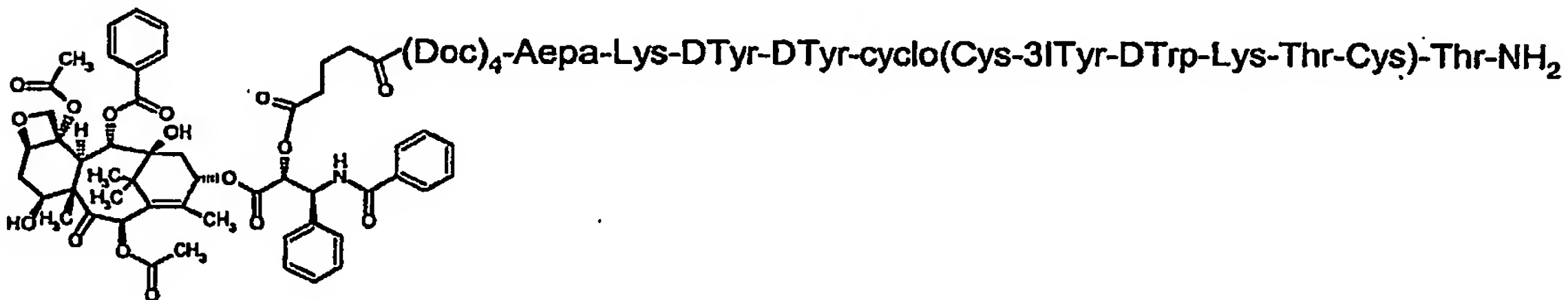
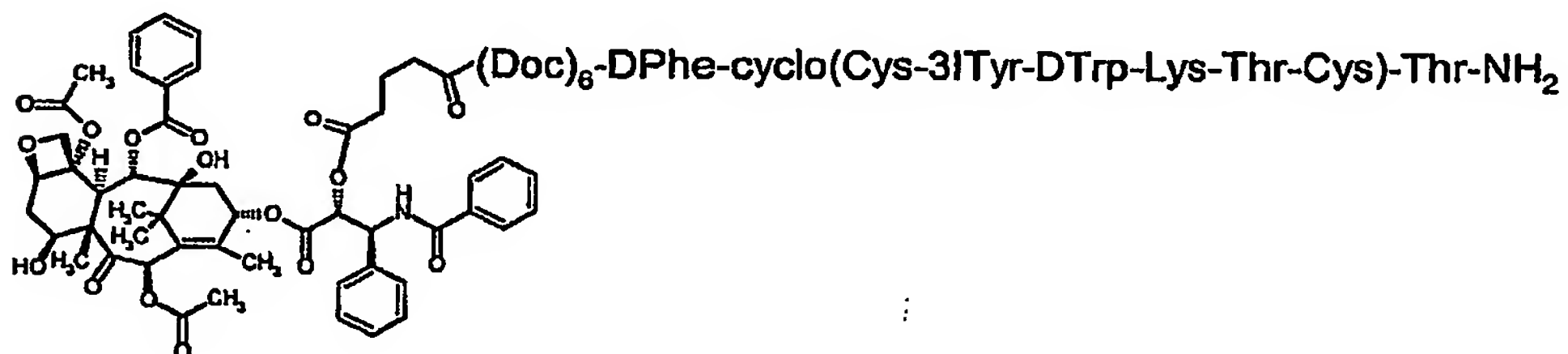
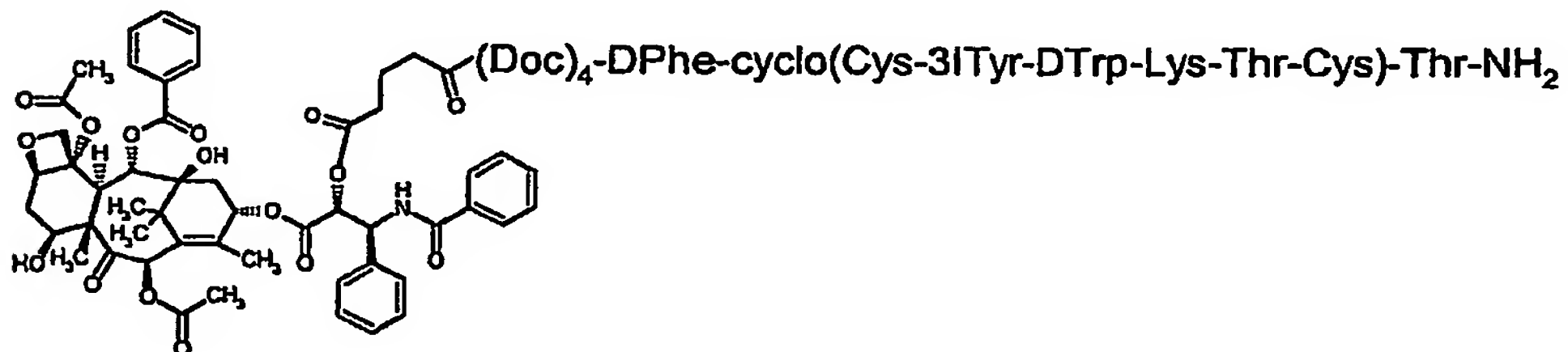
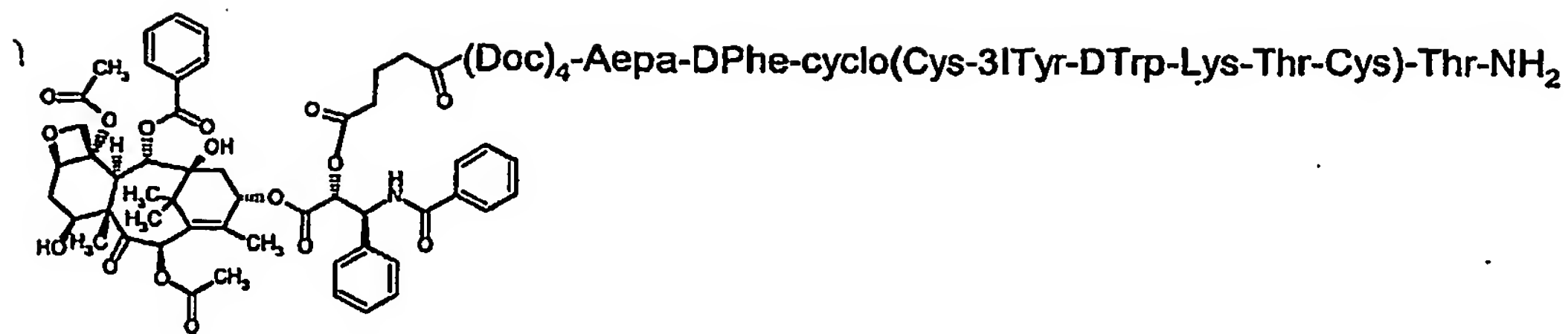


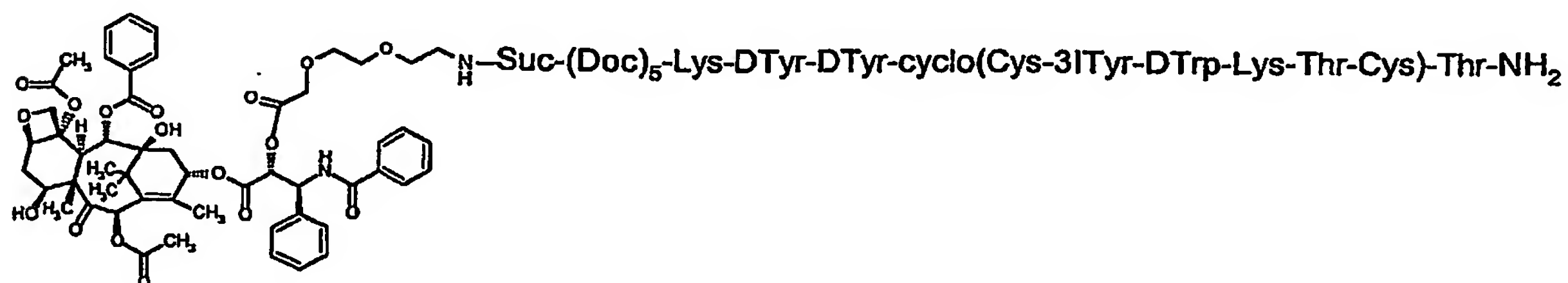
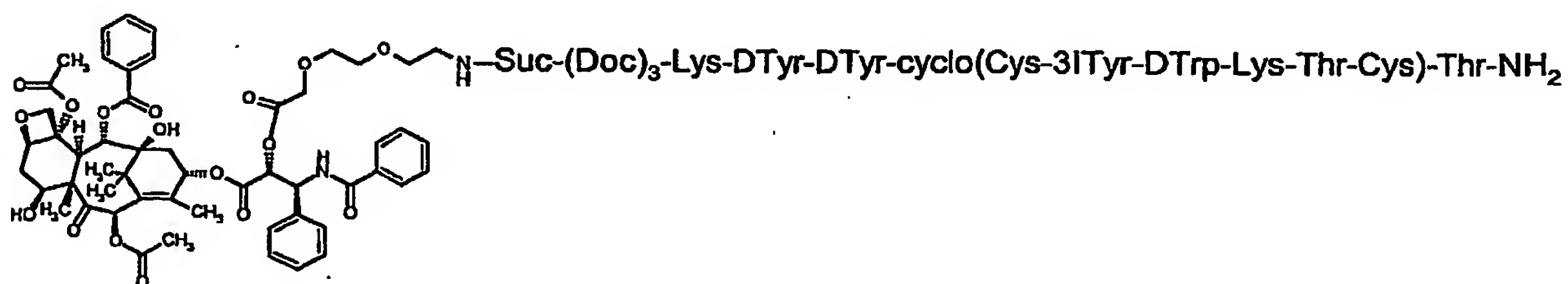
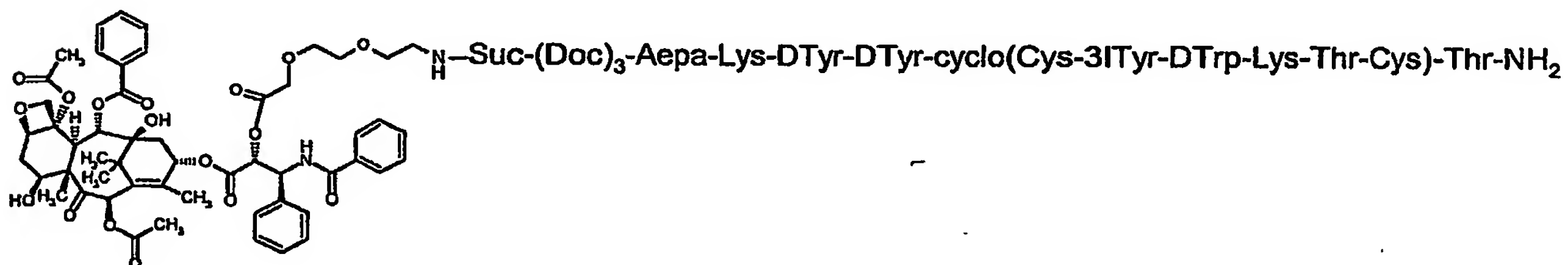
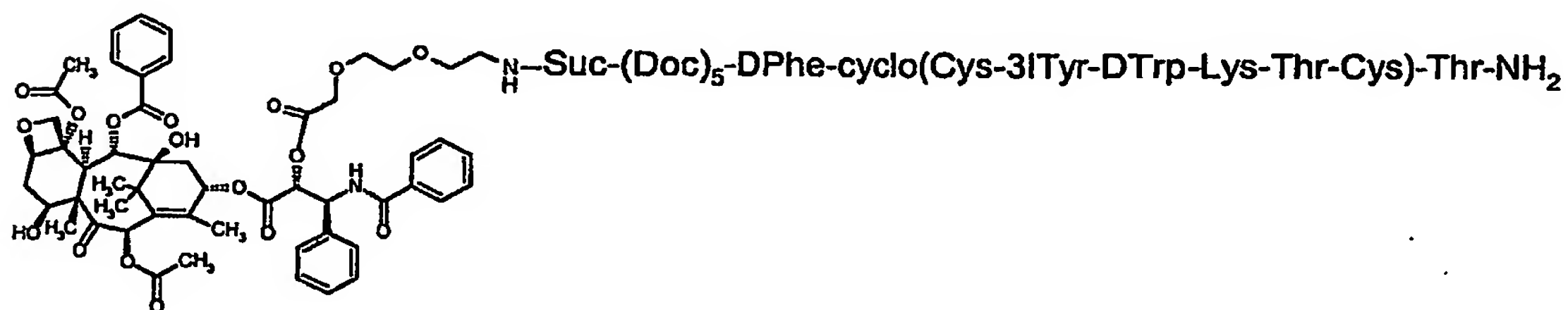
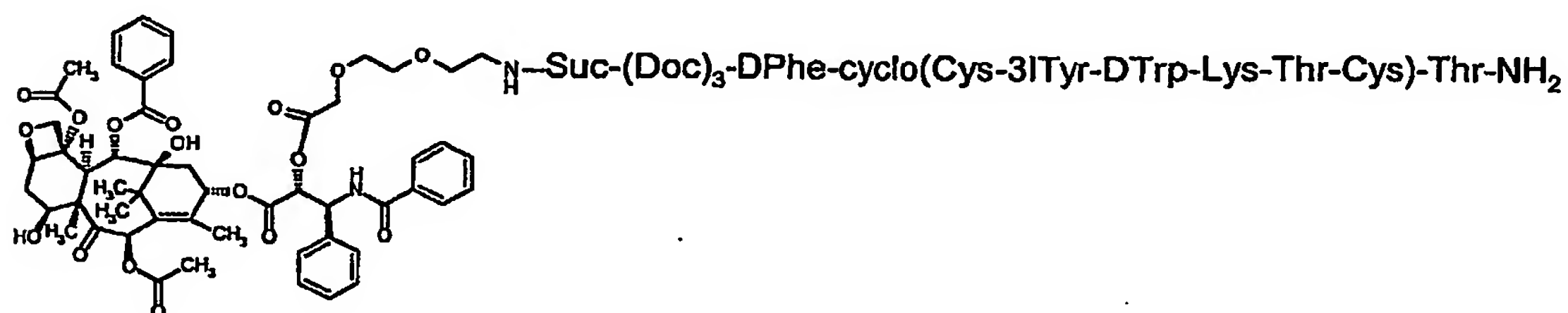
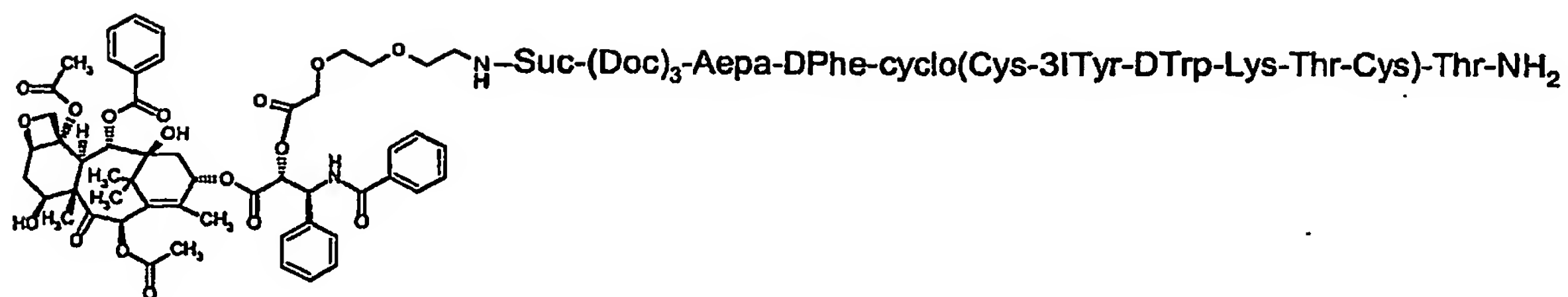


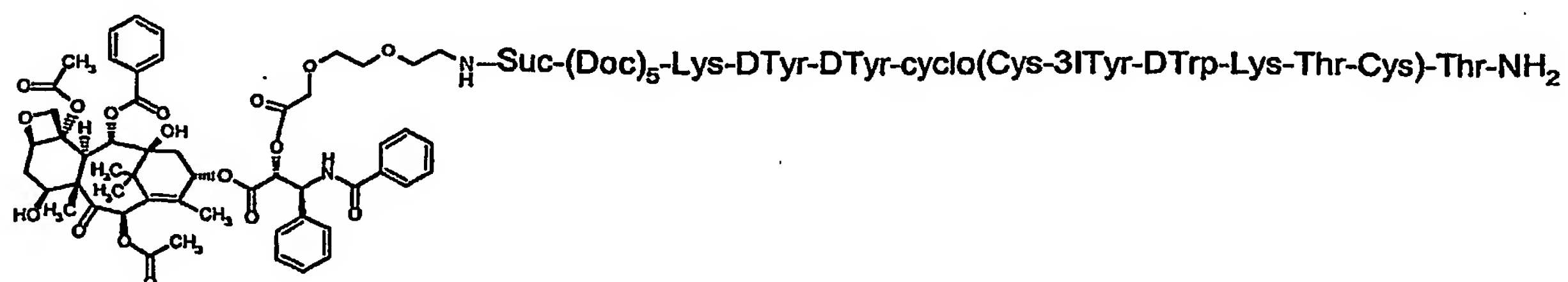
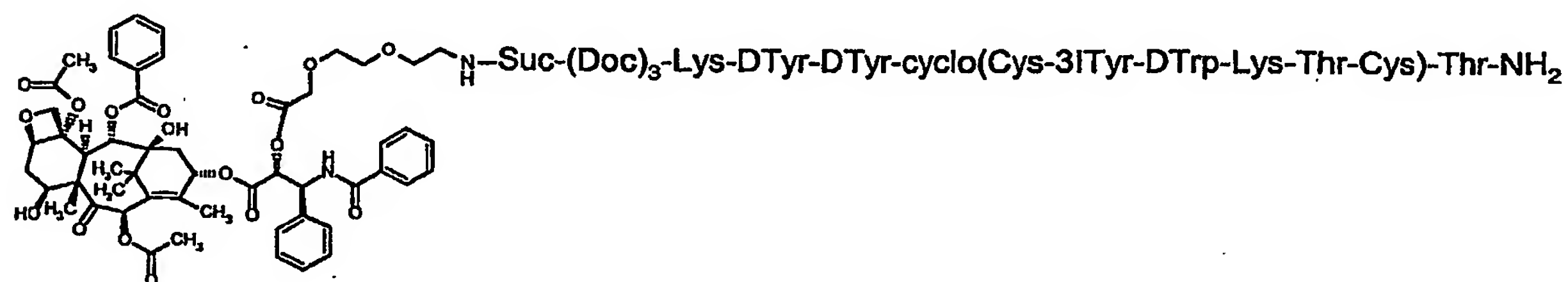
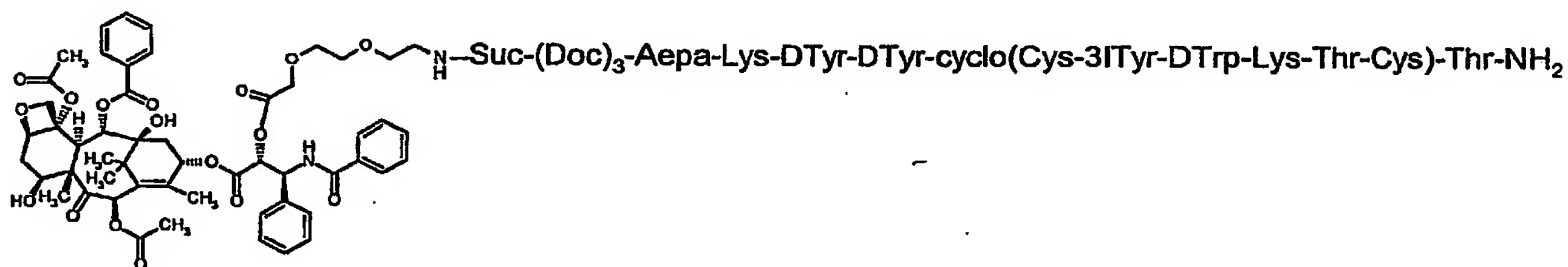
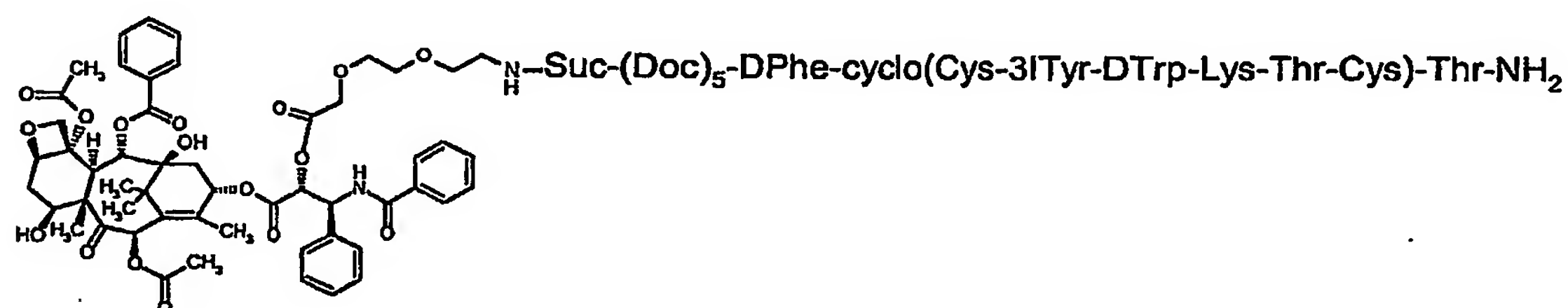
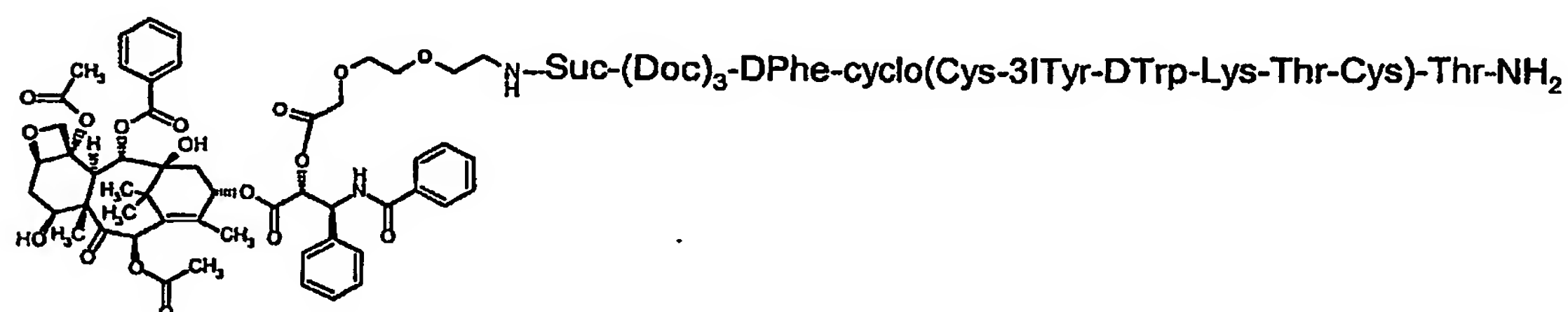
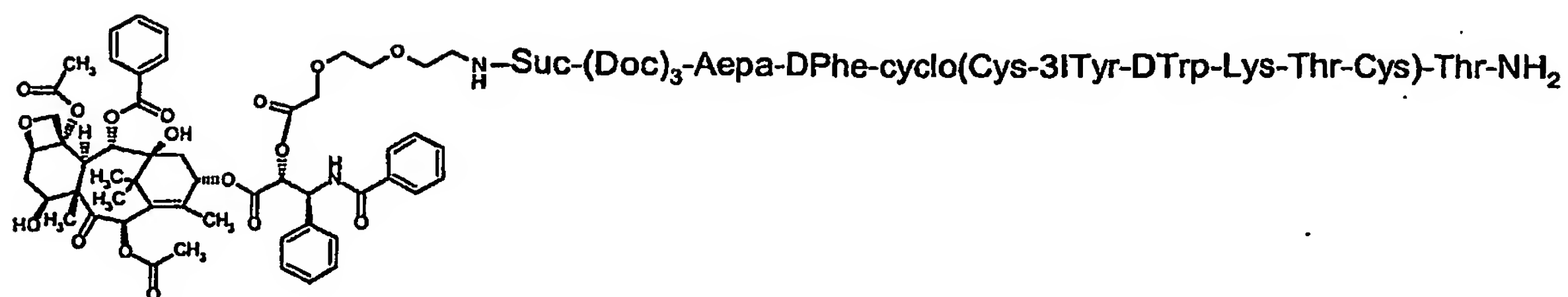
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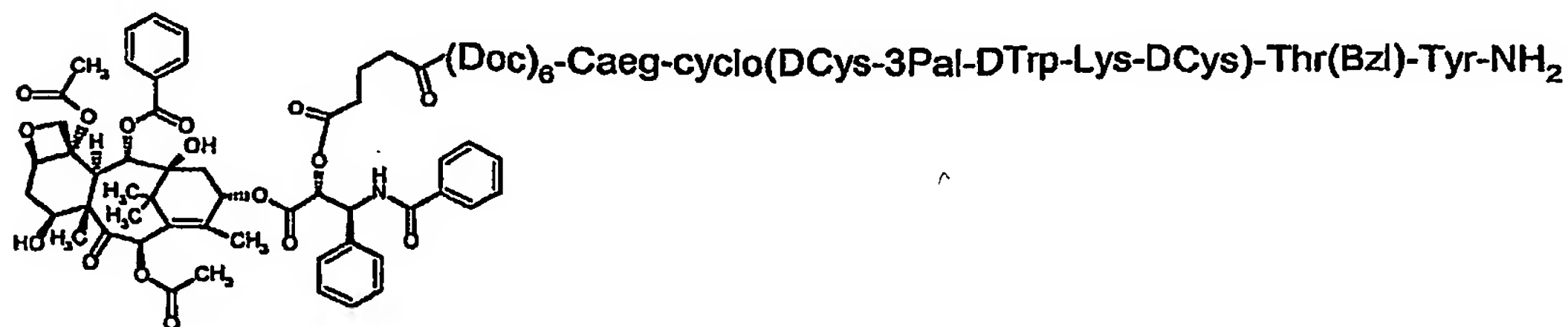
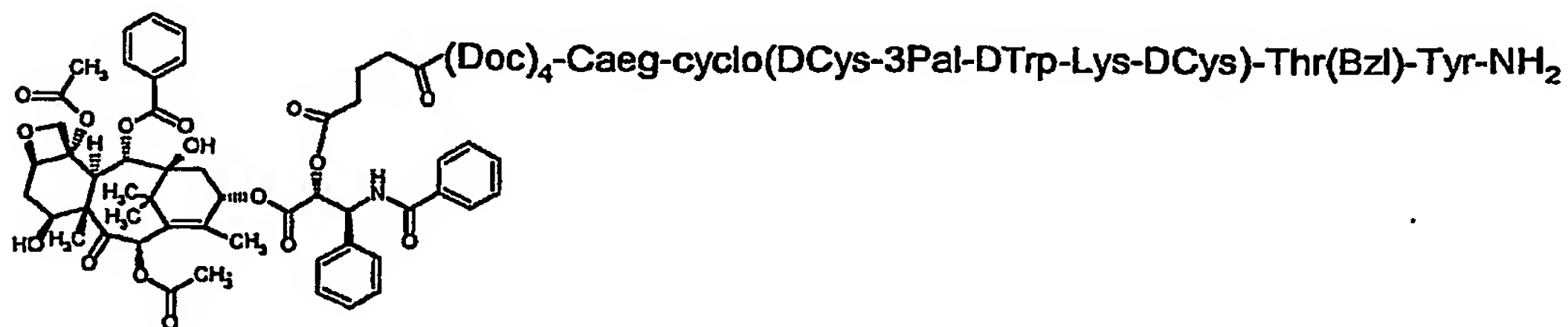
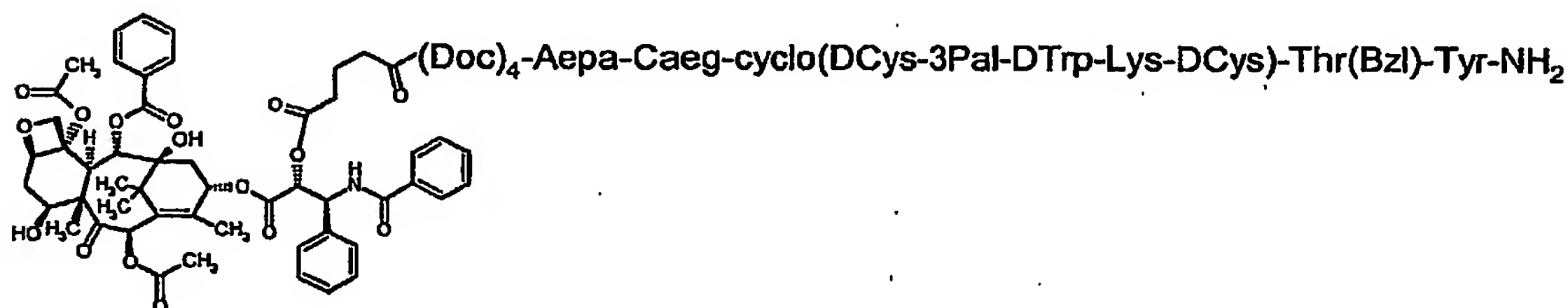
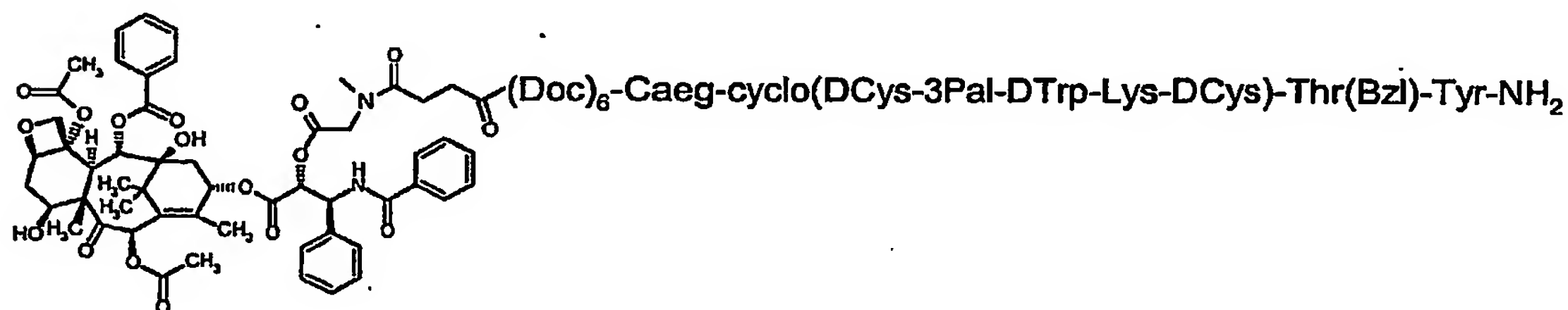
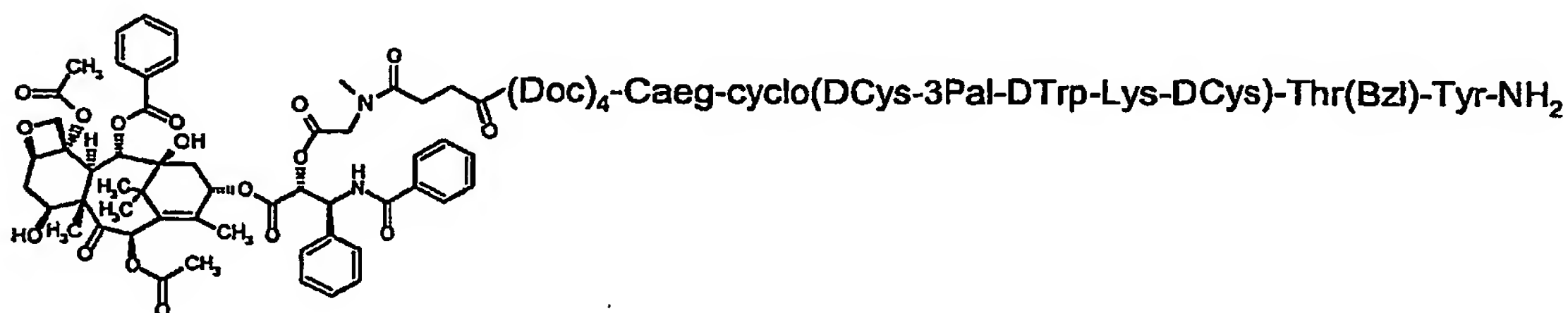
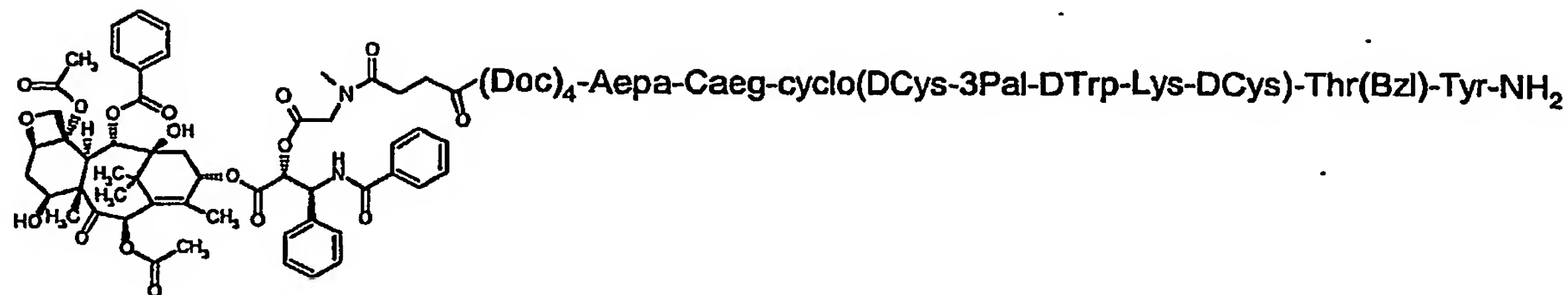


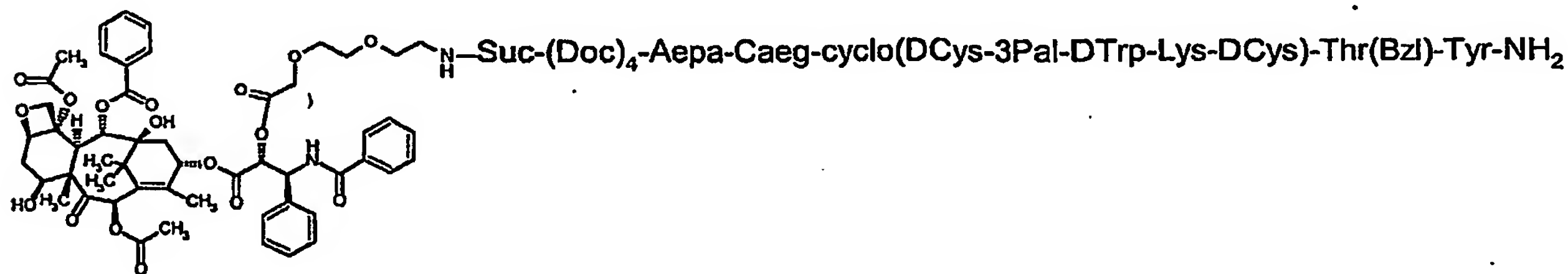
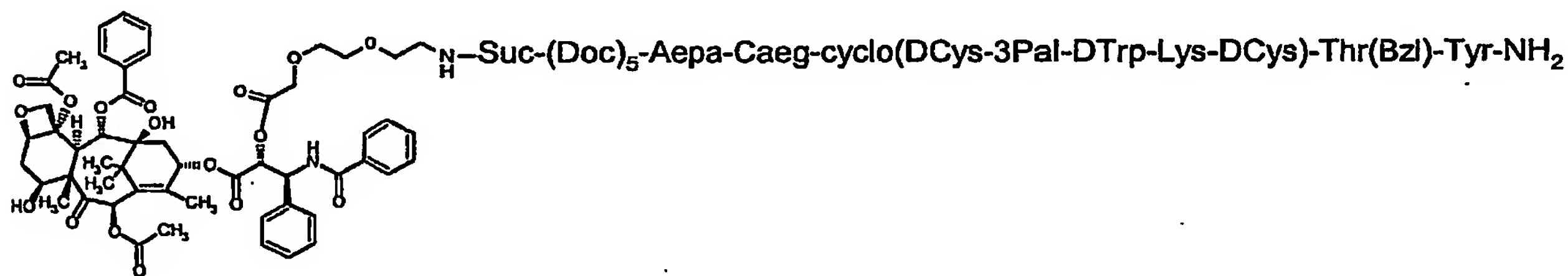
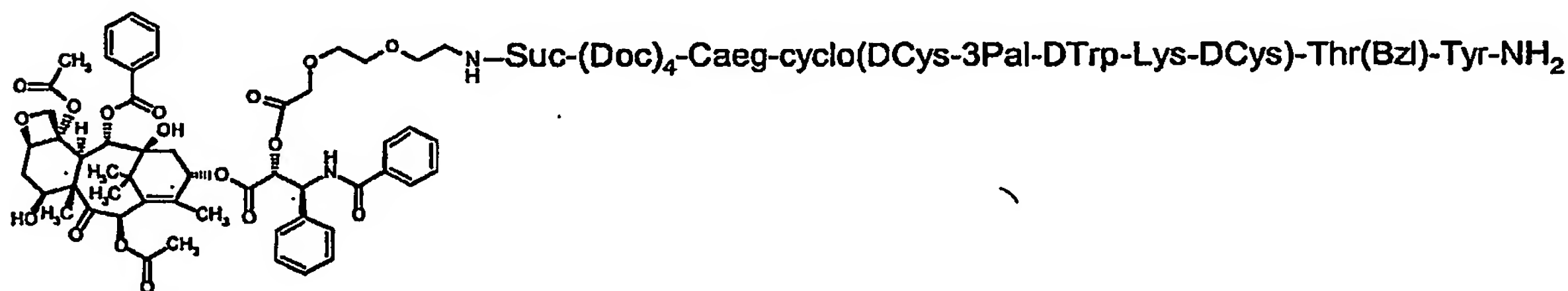
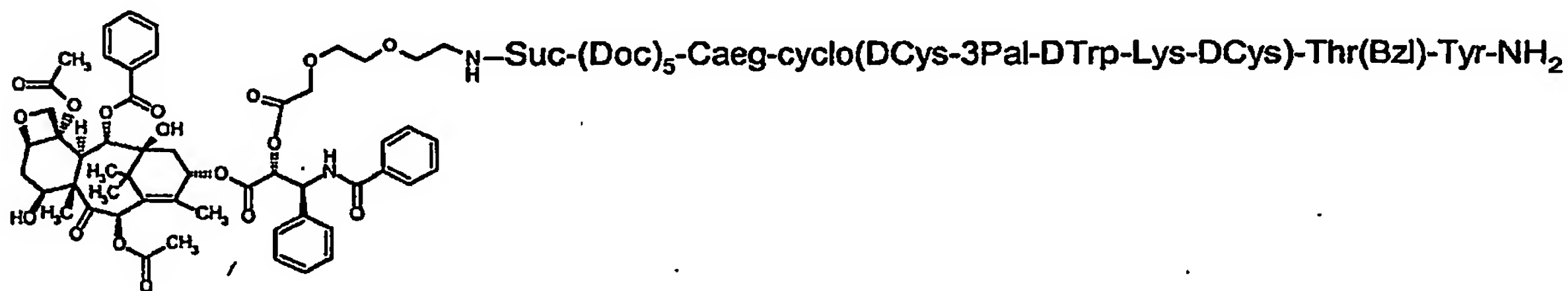
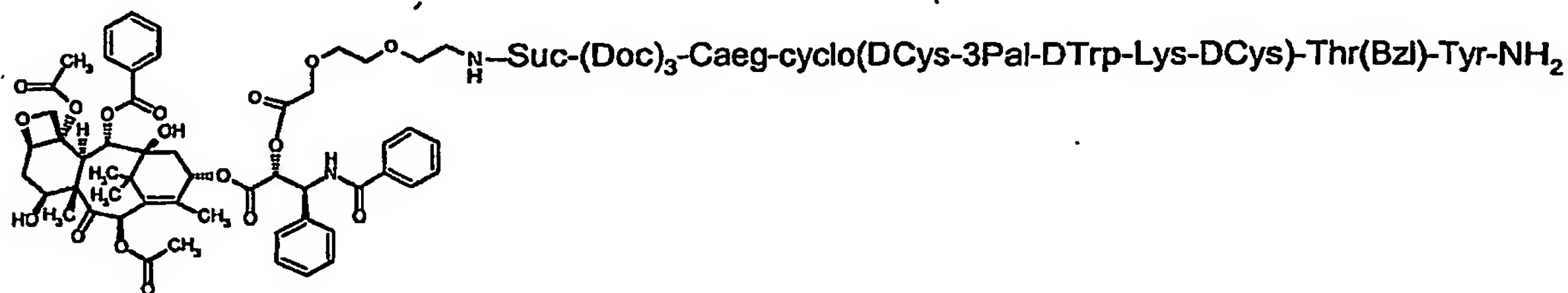
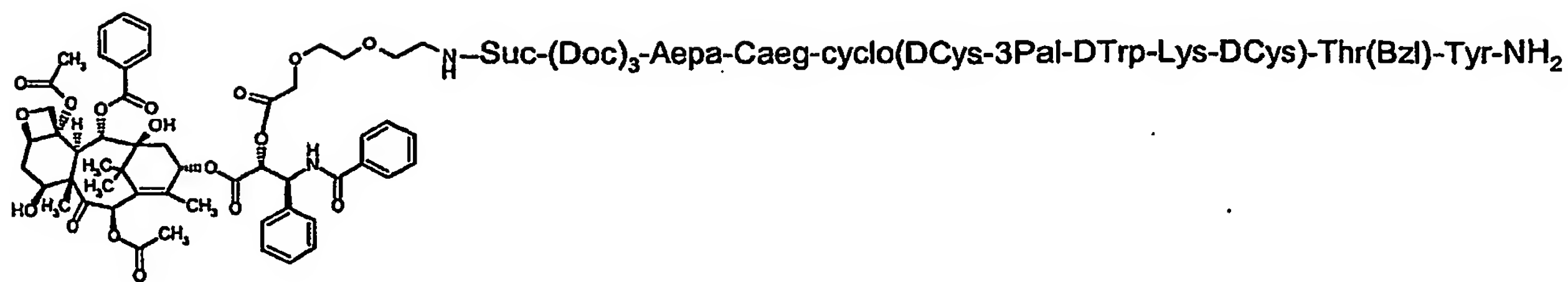












CLAIMS

1. A compounds according to formula (I):



(I)

wherein:

X is a cytotoxic or cytostatic agent;

each of B¹, B², B³, and B⁴ is, independently for each occurrence, (Doc)_m, (Aepa)_n, -(C(O)-A1-A2-A3-A4-A5-C(O))_s- or (amino acid)_p,

each of A1 and A5 is, independently for each occurrence, CR¹R²;

each of R¹ and R² is, independently for each occurrence, H, F, Br, Cl, I, C₍₁₋₃₀₎alkyl, C₍₂₋₃₀₎alkenyl, substituted C₍₁₋₃₀₎alkyl, substituted C₍₂₋₃₀₎alkenyl, SR³, S(O)R⁴, or S(O)₂R⁵, or R¹ and R² together can form a C₍₃₋₃₀₎cycloalkyl, C₍₃₋₃₀₎heterocycle, or C₍₅₋₃₀₎aryl ring;

each of R³, R⁴, and R⁵ is, independently for each occurrence, C₍₁₋₃₀₎alkyl, C₍₂₋₃₀₎alkenyl, substituted C₍₁₋₃₀₎alkyl, or substituted C₍₂₋₃₀₎alkenyl;

each of A², A³, and A⁴ is, independently for each occurrence, CR⁶R⁷, O, S, (CH₂)_t or absent;

each of R⁶ and R⁷, independently for each occurrence, H, F, Br, Cl, I, C₍₁₋₃₀₎alkyl, C₍₂₋₃₀₎alkenyl, substituted C₍₁₋₃₀₎alkyl, substituted C₍₂₋₃₀₎alkenyl, SR³, S(O)R⁴, or S(O)₂R⁵;

or R⁶ and R⁷ together may form a ring system;

m is, independently for each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

n is, independently for each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

p is, independently for each occurrence, 0, 1, or 2;

s is, independently for each occurrence, 1, 2, 3, 4, or 5;

t is, independently for each occurrence, 0, 1, 2, or 3;

Z is a ligand of a biological receptor, an analog thereof, or a derivative of said ligand or of said analog;

provided that:

when X is doxorubicin or a doxorubicin derivative, at least one of m and n is not 0; and

when X is paclitaxel or a paclitaxel derivative, then B¹ is (amino acid)_p and p is 1 or 2;

or a pharmaceutically acceptable salt thereof.;

2. A compound according to claim 1, wherein X is a cytotoxic moiety;

or a pharmaceutically acceptable salt thereof..

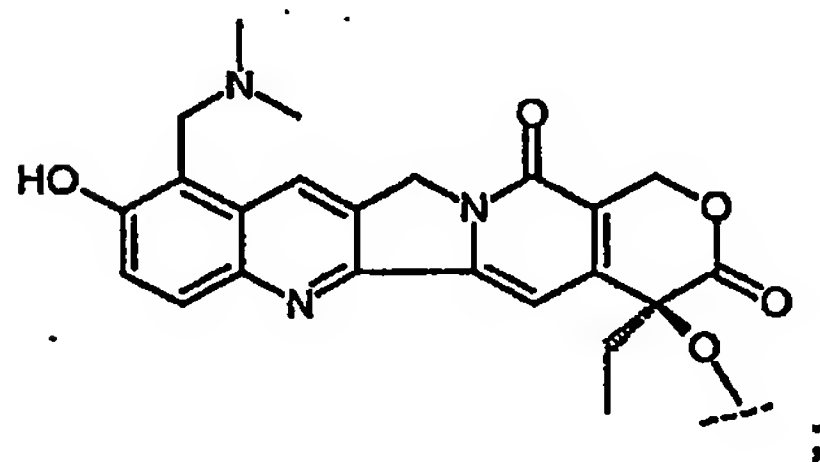
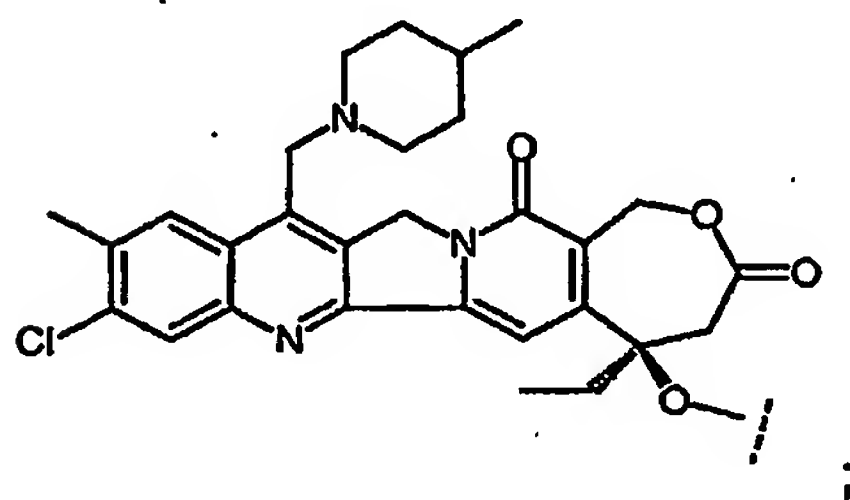
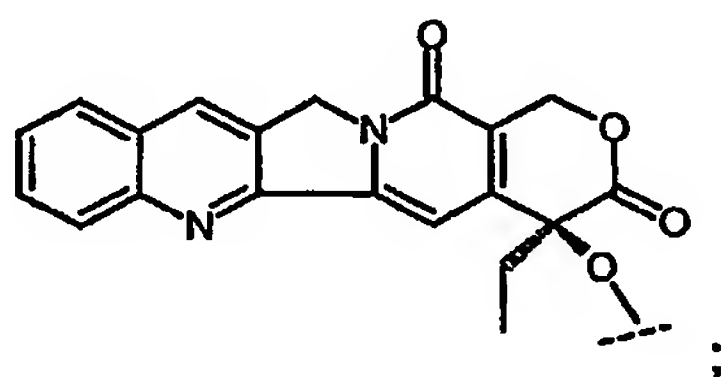
3. A compound according to claim 2, wherein X is an anthracycline;

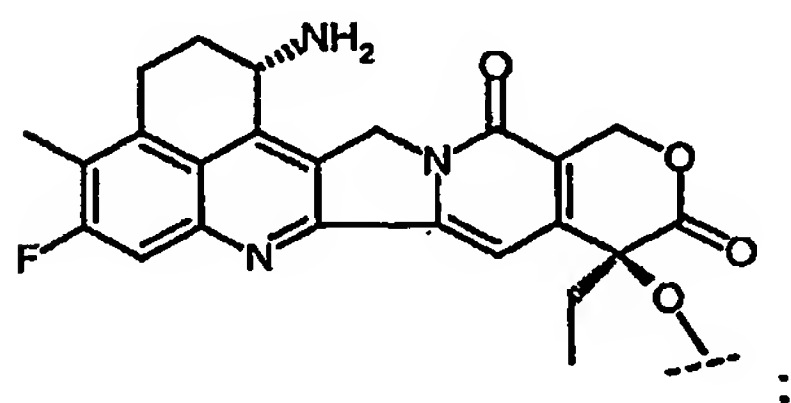
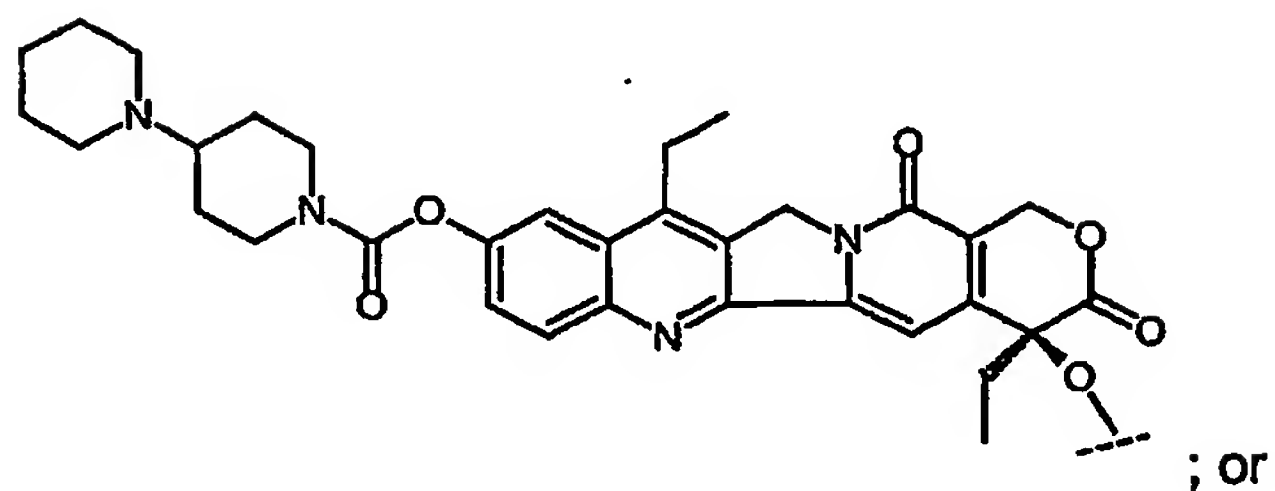
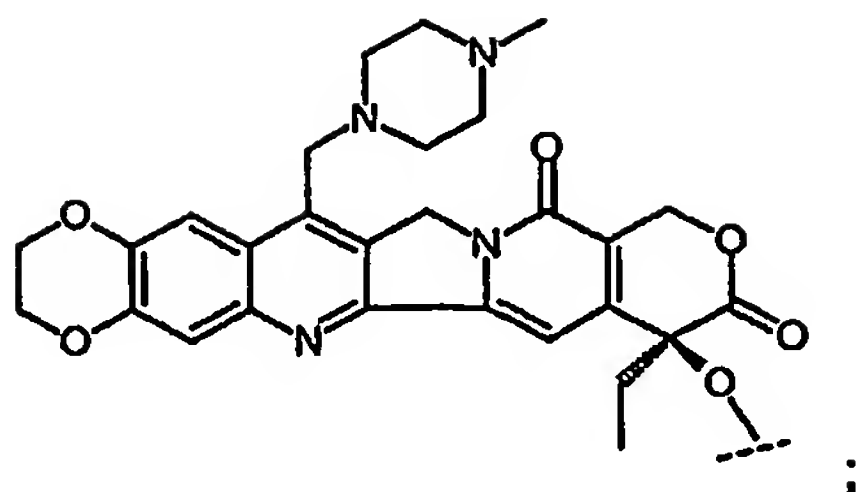
or a pharmaceutically acceptable salt thereof..

4. A compound according to claim 3, wherein X is camptothecin, a camptothecin derivative, paclitaxel, a paclitaxel derivative, doxorubicin, or a doxorubicin derivative;

or a pharmaceutically acceptable salt thereof.

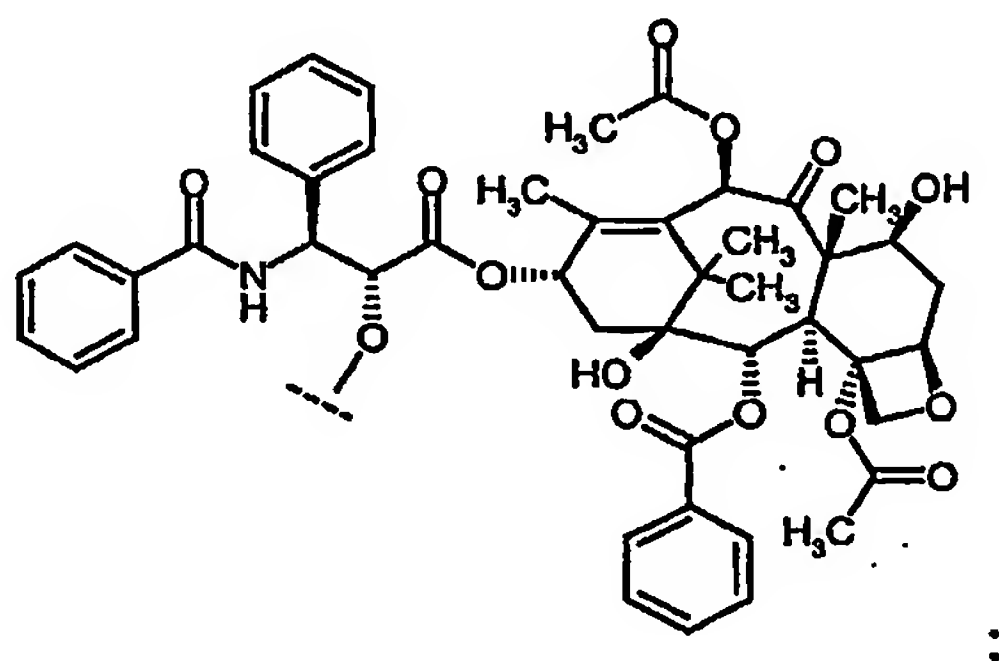
5. A compound according to claim 4, wherein X is camptothecin or a camptothecin derivative, wherein said camptothecin derivative is:





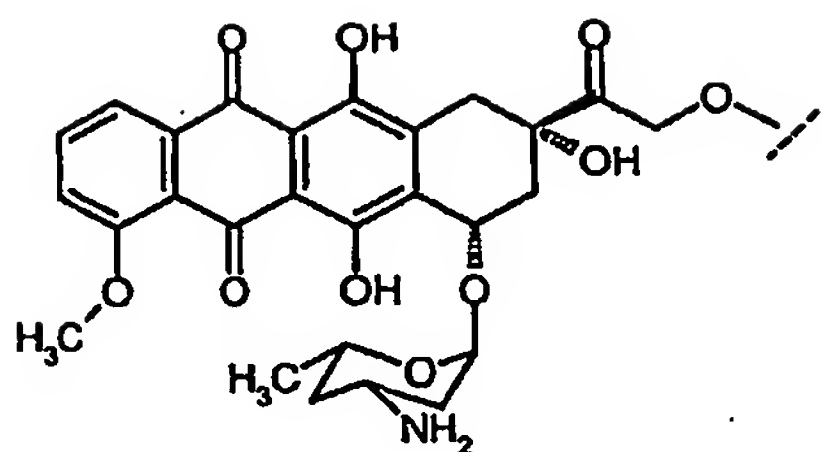
or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 4, wherein X is paclitaxel or a paclitaxel derivative, wherein said paclitaxel derivative is:



or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 4, wherein X is doxorubicin or a doxorubicin derivative, wherein said doxorubicin derivative is:



or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1-7, wherein Z is a somatostatin, a bombesin, or an LHRH, or an analog thereof, or a derivative of said ligand or of said analog; or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 8, wherein Z is a somatostatin analog according to the formula:

- DPhe-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;
- DPhe-cyclo(Cys-3ITyr-DTrp-Lys-Val-Cys)-Thr-NH₂;
- DPhe-cyclo(Cys-3ITyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;
- DPhe-cyclo(Cys-3ITyr-DTrp-Lys-Thr-Cys)-Thr-NH₂;
- Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;
- Caeg-cyclo(DCys-Pal-DTrp-Lys-DCys)-Thr(Bzl)-Tyr-NH₂;
- D2Nal-cyclo[Cys-Tyr-DTrp-Lys-Val-Cys]-Thr-NH₂;
- DPhe-cyclo[Cys-Phe-DTrp-Lys-Thr-Cys]-Thr-ol;
- cyclo({4-(-NH-C₂H₄-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4-Bzl)-Phe); or
- DPhe-cyclo[Cys-Tyr-DTrp-Lys-Val-Cys]-Trp-NH₂;

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 8, wherein Z is an LHRH analog according to the formula:

- Glp-His-Trp-Ser-Tyr-DLys(-)-Leu-Arg-Pro-Gly-NH₂;
- Glp-His-Trp-Ser-Tyr-DOrn(-)-Leu-Arg-Pro-Gly-NH₂;
- Glp-His-Trp-Ser-Tyr-DDab(-)-Leu-Arg-Pro-Gly-NH₂;

- Glp-His-Trp-Ser-Tyr-DDap(-)-Leu-Arg-Pro-Gly-NH₂;
- Glp-His-Trp-Ser-Tyr-DApa(-)-Leu-Arg-Pro-Gly-NH₂;
- Glp-His-Trp-Ser-Tyr-DLys(-)-Leu-Arg-Pro-NHEt;
- Glp-His-Trp-Ser-Tyr-DOrn(-)-Leu-Arg-Pro-NHEt;
- Glp-His-Trp-Ser-Tyr-DDab(-)-Leu-Arg-Pro-NHEt;
- Glp-His-Trp-Ser-Tyr-DDap(-)-Leu-Arg-Pro-NHEt;
- Glp-His-Trp-Ser-His-DLys(-)-Trp-Tyr-Pro-Gly-NH₂;
- Glp-His-Trp-Ser-His-DOrn(-)-Trp-Tyr-Pro-Gly-NH₂;
- Glp-His-Trp-Ser-His-DDab(-)-Trp-Tyr-Pro-Gly-NH₂; or
- Glp-His-Trp-Ser-His-DDap(-)-Trp-Tyr-Pro-Gly-NH₂;

or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 8, wherein Z is a bombesin analog according to the formula:

- Gln-Trp-Ala-Val-Gly-His-Leu- Ψ (CH₂;NH)-Leu-NH₂;
- Gln-Trp-Ala-Val-Gly-His-Leu- Ψ (CH₂;NH)-Phe-NH₂;
- Gln-Trp-Ala-Val- β Ala-His-Leu-Leu-NH₂;
- Gln-Trp-Ala-Val- β Ala-His-Leu-Nle-NH₂;
- Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH₂;
- Gln-Trp-Ala-Val-Gly-His-Phe-Met-NH₂;
- Gln-Trp-Ala-Val- β Ala-His-Phe-Nle-NH₂;
- Gln-Trp-Ala-Ala- β Ala-His-Phe-Nle-NH₂;
- Gln-Trp-Ala-Val- β Ala-His-Ala-Nle-NH₂;
- Gln-Trp-Ala-Val- β Ala-Ala-Phe-Nle-NH₂;
- Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH₂;
- DPhe-Gln-Trp-Ala-Val-Gly-His-Leu- Ψ (CH₂;NH)-Leu-NH₂;
- DPhe-Gln-Trp-Ala-Val-Gly-His-Leu- Ψ (CH₂;NH)-Phe-NH₂;

- DPhe-Gln-Trp-Ala-Val-βAla-His-Leu-Leu-NH₂;
- DPhe-Gln-Trp-Ala-Val-βAla-His-Leu-Nle-NH₂;
- DPhe-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH₂;
- DPhe-Gln-Trp-Ala-Val-Gly-His-Phe-Met-NH₂;
- DAla-Gln-Trp-Ala-Val-βAla -His-Phe-Nle-NH₂;
- DPhe-Gln-Trp-Ala-Val-βAla -His-Phe-Nle-NH₂;
- DPhe-Gln-Trp-Ala-Ala-βAla -His-Phe-Nle-NH₂;
- DPhe-Gln-Trp-Ala-Val-βAla -His-Ala-Nle-NH₂;
- DPhe-Gln-Trp-Ala-Val-βAla -Ala-Phe-Nle-NH₂; or
- DPhe-Gln-Trp-Ala-Val-Gly-His-Leu-Leu-NH₂;

or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 1 wherein at least one of m and n is not 0; or a pharmaceutically acceptable salt thereof.
13. A compound comprising the product of any one of examples 19-25, 28-32, 40-42, 45-65, and 74-75; or a pharmaceutically acceptable salt thereof.
14. A compound comprising an intermediate compound disclosed in any one of examples 1 - 75; or a pharmaceutically acceptable salt thereof.
15. A compound selected from the compounds listed in Appendix A, or a pharmaceutically acceptable salt thereof.
16. A compound selected from the compounds listed in Appendix B; or a pharmaceutically acceptable salt thereof.
17. A compound selected from the compounds listed in Appendix C; or a pharmaceutically acceptable salt thereof.
18. A compound selected from the compounds listed in Appendix D; or a pharmaceutically acceptable salt thereof.
19. A compound selected from the compounds listed in Appendix E; or a pharmaceutically acceptable salt thereof.

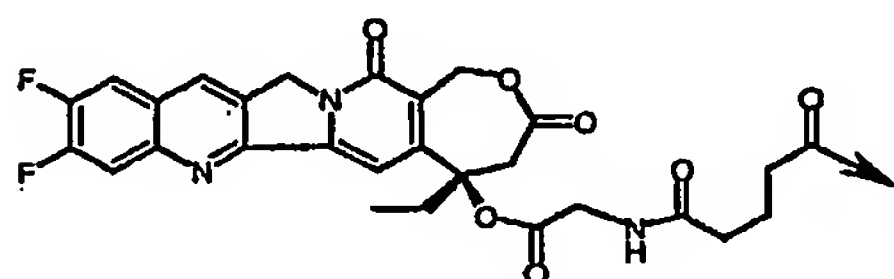
20. A compound selected from the compounds listed in Appendix F; or a pharmaceutically acceptable salt thereof.

21. A compound selected from the compounds listed in Appendix G; or a pharmaceutically acceptable salt thereof.

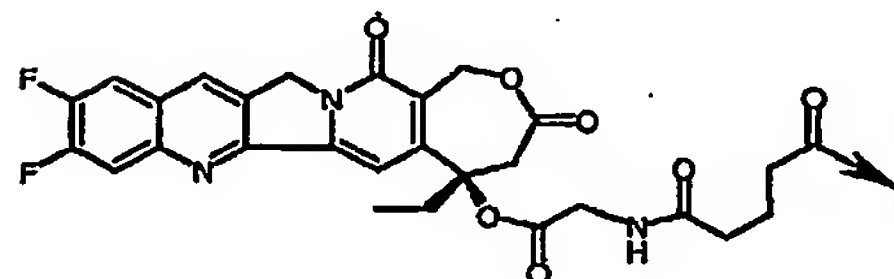
22. A compound selected from the compounds listed in Appendix H; or a pharmaceutically acceptable salt thereof.

23. A compound selected from the compounds listed in Appendix I; or a pharmaceutically acceptable salt thereof.

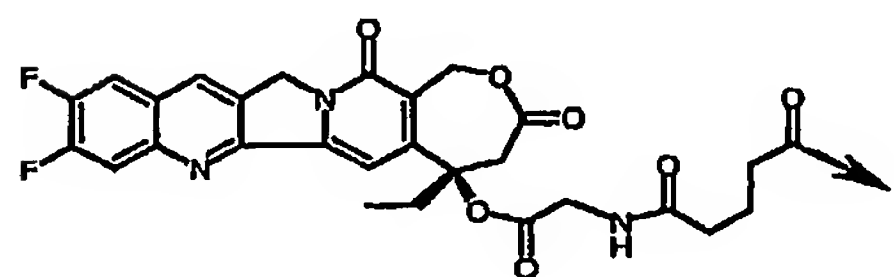
24. A compound according to the formula:



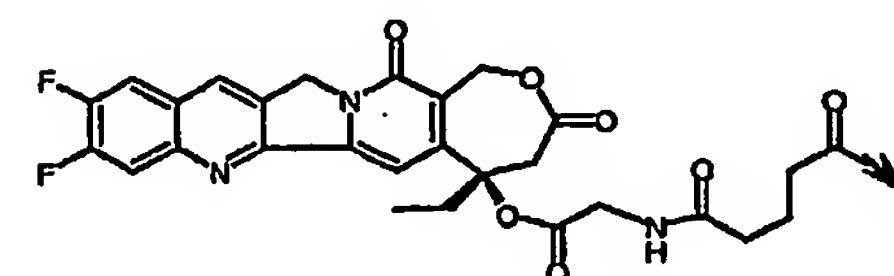
- (Doc)₄-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;



--(Doc)₆-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;



--Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂;



--Aepa-Lys-DTyr-DTyr-cyclo(Cys-Tyr-DTrp-Lys-Abu-Cys)-Thr-NH₂ ;

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